



# Sleep Disorders in Neurology

A PRACTICAL APPROACH

Edited by

Sebastian Overeem and Paul Reading

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A practical approach

EDITED BY

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# Foreword

When I was a medical student, then a junior hospital doctor, then a trainee neurologist and even when I was a young consultant neurologist I did not take a sleep history from patients if the problem was neither insomnia nor excessive daytime sleepiness. In practice – back then – insomnia did not come to neurologists anyway and still mostly doesn't unless maybe restless legs are an issue, and excessive daytime sleepiness was all but synonymous with the narcolepsy syndrome in the days before sleep apnoea and other sleep-related breathing disorders were popularised and we all were alerted to how common they were. 'How do you sleep?' and 'do you snore?' were just not amongst the routine questions one asked of neurology patients, but of course we always enquired about blackouts, headache, double vision and so on. Also neurologists were perhaps more than a little unwilling to sit up all night with patients in the days before video and all the other sophisticated monitoring equipment became available (paradoxically though it is still the history from the patients and any bed partner that counts more than the tests, at least for neurology rather than sleep-related breathing disorders). And maybe sleep problems were regarded as more of an amusing foible than needing proper attention.

But these days sleep, the lack of it, and too much of it, is everywhere in neurology. And parasomnias are now recognised as an important differential diagnosis for nocturnal epilepsy. Indeed, if difficult parasomnias are not sent to a neurologist who else is going to sort them out? I don't think this new found interest is 'disease mongering' stirred up by the pharmaceutical industry but a reflection of important and frequent symptoms that we missed – or simply ignored – in past times.

Sleep problems do hover slightly uneasily between neurologists and respiratory physicians who clearly have to work together to provide a specialised service; their skills and knowledge are complementary. But this book's focus is on the needs of neurologists and neurological rather than respiratory problems, edited by a sleep physician and a general neurologist with a sub specialist interest in sleep.

It is extraordinary how common sleep problems are in neurology patients, and how we just did not recognise them until relatively recently – maybe

we just 'switched off' when patients and their relatives tried to tell us about symptoms which we were unfamiliar with and so didn't make a lot of sense, either for diagnosis or management. I hope this book will help neurologists deal better with sleep problems as well as the other more traditional symptoms that their patients may have.

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January 2010

# Preface

There are those who predict that medical textbooks will shortly become the extinct “dinosaurs” of information transfer and education. Indeed, the global availability of knowledge and thirst for brand-new data, the inevitable delays in producing written multi-authored texts, the expense of books together with the demise of traditional libraries would all appear to support this contention. In a rapidly changing environment, therefore, books, like dinosaurs, need to evolve in parallel and certainly be clearer in their aims than previously. Edited by a sleep physician and a general neurologist with a subspecialist interest in sleep, this book was conceived as a counterpoint to the established large encyclopedic reference volumes currently available. The intentions were to cover areas not always addressed by standard sleep medicine or, indeed, neurology textbooks, at least from a practical perspective. The book is aimed at clinicians and healthcare professionals not specifically trained or experienced in sleep medicine who nevertheless need to manage neurologically damaged patients with increasingly recognized sleep-wake disturbances. As such, we envisage the book will serve as an easily digested and practical handy companion, rather than as an exhaustive and fully referenced factual tome.

Largely for historical reasons, most neurologists receive little formal training in academic and clinical aspects of sleep medicine. Most sleep units are run solely by physicians primarily interested in breathing-related sleep disorders and patients under their care may have little access to neurological expertise. This may seem paradoxical given conditions such as narcolepsy that are clearly “neurological” with recently defined specific neuropathology and neurochemistry. The lack of exposure to sleep medicine naturally tends to produce neurologists with an unconfident, at best, or nihilistic, at worst, approach to sleep-related symptoms in the clinic. By necessity, the situation is changing, especially given the increasingly recognized relevance of poor sleep or impaired wakefulness to the quality of life for chronic neurological patients. Furthermore, it is clear to most clinicians that deterioration in sleep often coincides with or even causes worsening control of many chronic neurological conditions such as epilepsy.

Most neurologists are not referred cases of primary insomnia or obvious obstructive sleep apnea but may well encounter them incidentally. Despite their high prevalence, there is little emphasis on these common sleep disorders in this book and the focus is on those specific symptoms commonly experienced by neurological patients, assuming they are asked about them.

When sleep “goes wrong” it impacts highly on all aspects of a subject’s well-being and often their carer’s. As a result, increasing attention to patient choice has appropriately led to a higher expectation that such symptoms should be taken seriously. However, many neurologists with traditional approaches might feel that sleep problems are not disabling enough to warrant detailed attention. We would counter-argue that “sleep is for the brain” and without enough of it, the brain suffers. It is perhaps worthwhile recalling somewhat distasteful experiments from the late nineteenth century demonstrating that puppies could survive longer without water than without sleep.

The reputation that neurology is a discipline in which successful therapeutic options play second fiddle to diagnostic acumen is only partly true. Perhaps counterintuitively, treating sleep symptoms in neurology is often particularly rewarding, patients and carers appreciating even partial improvements in controlling their sleep-wake cycle. A recurrent theme in the book is that drugs to improve sleep are often selected using “medicine-based” evidence and personal experience rather than the gold standard of evidence-based medicine. Despite this, together with the relative limited armamentarium of drugs available to the sleep physician, we believe the majority of patients can be helped with a flexible and pragmatic approach. When drugs are mentioned, their proposed use is often “off license” and any prescriber will need to take responsibility for monitoring and progress. Similarly, doses of drugs are often approximate recommendations and it is not intended to provide strict or didactic guidelines. In many of the sleep-disordered populations covered in the book, it is appropriate to suggest long-term therapy on the assumption that spontaneous improvement is unlikely. This often needs to be emphasized to primary care physicians who are more accustomed to providing short-term prescriptions for sleep-related problems.

The point or threshold at which a general neurologist should engage the help of a sleep specialist clearly depends on a number of factors. However, an exchange of views and expertise in a multidisciplinary setting, if possible at an early stage, would seem to be the best approach if facilities allow. We would encourage neurologists to forge stronger links with physicians more dedicated to sleep medicine in the firm belief any “cross fertilization” will benefit both sides.

By necessity, there is some overlap in the topics covered by some chapters. However, given the personal and practical approach we have espoused throughout the book, we hope different perspectives will improve rather than hinder understanding and effective symptom management in sleep-disordered neurological patients.

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## **PART I**

# Diagnosis of Sleep Disorders

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## CHAPTER 1

# The sleep history

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## Introduction

It is a commonly held misperception that practitioners of sleep medicine are highly dependent on sophisticated investigative techniques to diagnose and treat sleep-disordered patients. To the contrary, with the possible exception of sleep-related breathing disorders, it is relatively rare for tests to add significant diagnostic information, provided a detailed and accurate 24-hour sleep-wake history is available. In fact, there can be few areas of medicine where a good, directed history is of more diagnostic importance. In some situations, this can be extremely complex due to potentially relevant and interacting social, environmental, medical, and psychological factors. Furthermore, obtaining an accurate sleep history often requires collateral or corroborative information from bed partners or close relatives, especially in the assessment of parasomnias.

In sleep medicine, neurological patients can present particular diagnostic challenges. It can often be difficult to determine whether a given sleep-wake symptom arises from the underlying neurological disorder and perhaps its treatment or whether an additional primary sleep disorder is the main contributor. The problem is compounded by the relative lack of formal training in sleep medicine received by the majority of neurology trainees that often results in reduced confidence when faced with sleep-related symptoms. However, it is difficult to underestimate the potential importance of disordered sleep in many chronic neurological conditions such as epilepsy, migraine, and parkinsonism.

The following framework is a personal view on how to approach sleep-wake complaints from a neurological perspective. Although the focus is on individual or particular symptoms, it should be realized that several conditions can produce a variety of symptoms across the full 24-hour sleep-wake

period. In chapters 2 and 3, the various ways in which sleep can be recorded are discussed. Finally, in chapter 4, an “integrative” approach to diagnosis is outlined, illustrated by case examples.

### **Excessive daytime sleepiness**

Excessive daytime sleepiness (EDS) is an increasingly recognized symptom deemed worthy of assessment. It is relatively prevalent and disabling both in general and neurological populations [1]. A not uncommon question posed to general neurologists is whether a sleepy patient might have narcolepsy or a similar primary sleep disorder. Furthermore, “secondary” or “symptomatic” narcolepsy is evolving as a valid concept given recent major advances in unraveling the neurobiology of sleep regulation. In particular, a variety of pathologies predominantly affecting the hypothalamus can mimic elements of idiopathic or primary narcolepsy [2].

In the initial assessment of EDS, it is essential to gain an impression of the severity of symptoms and how they are impacting on the subject. It is also crucial to confirm that the complaint is that of true excessive somnolence rather than simple fatigue or lethargy. Although sleepiness questionnaires are widely used and can act as an effective screening tool in this respect, they rarely help with actual diagnosis. Asking a subject about particularly unusual or inappropriate sleep episodes can therefore provide valuable insight. Habitual mid-afternoon or late evening naps when unoccupied could be considered normal phenomena, whereas regularly dropping to sleep mid-morning or in public places usually indicates a problem. A history of invariably napping as a car passenger for journeys of over an hour may suggest pathological levels of sleepiness. In narcolepsy, the subject may describe sleep onset even while engaged in physical activities such as writing or standing. Furthermore, in severe EDS, the subject may report awakening from naps unaware of any prior imperative to sleep. So-called “sleep attacks” are recognized in narcolepsy and have been widely reported in sleepy parkinsonian patients. Regarding the latter population, recent evidence suggests that they may be particularly poor at monitoring their levels of subjective sleepiness, making the history from relatives particularly important [3].

The commonest causes of mild and severe EDS are probably insufficient sleep and poor-quality overnight sleep, respectively (see chapter 19). A directed history, perhaps backed by a sleep diary, usually helps in diagnosing the former and can indicate causes of the latter. If a subject regularly reports at least 7 or 8 hours of continuous sleep yet remains significantly somnolent during the day, it is most likely that there is a disturbance of sleep architecture and, usually, that insufficient deep or restorative sleep is

being obtained. An overabundance of light (stage 2) sleep compared to deep non-REM sleep (stages 3 and 4) is frequently seen in sleep-related breathing disorders and periodic limb movement disorder. These diagnoses can easily be missed from the history if the subject is not a typical phenotype for the former or if they sleep alone. However, leading questions such as “do you invariably awake with a dry mouth?” or “are the bed clothes usually disrupted on waking?” can provide diagnostic clues. Morning headaches or general sensations of “heaviness” are traditionally associated with obstructive sleep apnea although are equally common in a variety of sleep disorders.

A drug history including alcohol habit is also clearly relevant in assessing EDS as numerous agents given before bed may appear to induce drowsiness and aid sleep onset but actually worsen nocturnal sleep quality overall. Tricyclic preparations and benzodiazepines are frequently associated with unrefreshing sleep yet are frequently given primarily as hypnotic agents. It is worth noting that most antidepressants will potentially worsen restless legs syndrome or periodic limb movement disorder (see chapter 8).

Less recognized causes of disturbed nocturnal sleep may be picked up by a focussed history. Nocturnal pain, frequent nocturia, persistent wheeze, and acid reflux are usually fairly obvious “toxins” to sleep and are generally readily reported. However, more subtle phenomena such as teeth grinding (bruxism) may not be recognized by the subject and only suspected if direct questions are asked about teeth wear, temporomandibular joint dysfunction, or jaw pain, especially on waking.

A number of primary neurological disorders, including narcolepsy, disrupt the continuity of nocturnal sleep most likely as a result of pathology in various brain regions intimately involved in sleep-wake control. A new symptom of sleep fragmentation and daytime somnolence in a patient with inflammatory brain disease such as multiple sclerosis, for example, might sometimes suggest inflammatory pathology in the pontomedullary area [4] or around the hypothalamus [5]. Idiopathic Parkinson’s disease is strongly associated with EDS, especially in the advanced stages. Although there are many potential causes, including dopaminergic medication, primary Lewy body brainstem pathology itself is a likely substrate for most of the sleep-wake dysregulation, especially with regard to REM sleep [6]. If a neurological patient complains of significant EDS and no obvious cause such as Parkinson’s disease is determined after a detailed history and subsequent sleep investigations, magnetic resonance brain imaging can be justified to exclude unexpected inflammatory or even structural pathology. This may particularly apply to sleepy, overweight children, for example [7].

There are usually sufficient clues from a patient’s history to suggest a specific diagnosis of narcolepsy, the quintessential primary disorder of sleep-wake dysregulation (chapter 19). Typically, narcolepsy causes

symptoms from early adolescence and profound delays in receiving a diagnosis are still commonplace. A detailed history, therefore, exploring issues of excessive sleepiness around schooling can be illuminating. Apart from its severity, the nature of sleepiness is not particularly exceptional or unique in narcolepsy. However, even short naps, planned or unplanned, tend to be restorative, allowing a “refractory” wakeful period of 3–4 hours. Given that REM sleep is particularly dysregulated in narcolepsy, it is also useful to enquire about the presence of dreams, dream-like experiences, or sleep paralysis during short naps. Even when alert, the majority of narcoleptics will be prone to automatic behaviors and reduced powers of concentration or vigilance, potentially reflecting brief “micro-sleeps.” These can be explored from a full history. Losing objects around the house or placing inappropriate objects in the fridge are particularly common examples of this phenomenon.

Cataplexy is present in two-thirds of narcoleptics and is very rarely seen in other situations. It is therefore an extremely specific phenomenon and important to recognize with confidence. Full-blown episodes of temporary paralysis triggered by positive emotions or their anticipation are generally easy to pick up from the history. Subtle or atypical variants may be missed, however, especially since “going weak” with laughter or other strong emotions is probably a normal phenomenon. Typically, cataplexy occurs in a relaxed or intimate environment in the company of friends or family. It is usually manifested by descending paralysis in a rostrocaudal direction over 2 or 3 seconds, preceded by head bobbing or facial twitching. Subjects often learn to anticipate the situations in which they are at risk of attacks and may even develop social phobias as a result. Common precipitants include positive emotions such as surprise at meeting an old acquaintance or watching comedy on television. Some report that the anticipation of a positive emotion, perhaps as a punchline is approaching, acts as the most potent stimulus. Negative emotions such as frustration, particularly that induced by children or pets, can also induce episodes in many. Partial attacks can be missed or hidden. Indeed, minor facial twitching, head bobbing, mild neck weakness, or a stuttering dysarthria when telling a joke may reflect the only observable manifestations of cataplexy. On the other hand, cataplexy is a doubtful explanation if episodes are very sudden or prolonged. Similarly, if consciousness levels are significantly impaired or if injuries frequently incurred during attacks, alternative diagnoses need consideration.

Nocturnal symptoms in narcolepsy are extremely varied but frequently significant. Often to the surprise of physicians inexperienced with narcolepsy, restless sleep with impaired sleep maintenance and even sleep-onset insomnia is common, as are excessive limb movements during sleep. The latter may reflect simple restlessness or periodic limb movements.

Many narcoleptics also exhibit dream enactment during REM sleep although it generally appears as a more benign phenomenon than that commonly seen in neurodegenerative disease [8]. In particular, the movements tend to be less explosive or violent in narcolepsy and there is not the striking male predominance as observed in Parkinson's disease, for example.

Unpleasant dreams that are particularly vivid and difficult to distinguish from reality are commonplace in narcolepsy. Indeed, narcoleptic children often become fearful of sleep as a result, so-called "clinophobia." Frank hallucinatory experiences in a variety of modalities including tactile may not be mentioned spontaneously through fear of being labeled mentally ill. These experiences are commonest around the sleep-wake transition periods or in states of drowsiness. A full history should therefore actively explore dream-like experiences in detail.

A less common sleep disorder, idiopathic hypersomnolence (IH), can often mimic narcolepsy although certain historical pointers may help with the differential diagnosis [9]. Idiopathic hypersomnolence in its classical form is characterized by long yet unrefreshing overnight sleep with prolonged napping during the day and continual sensations of reduced alertness. Difficulty in morning waking or prolonged confusion on forced waking are typical symptoms as are frequent acts of automatic behavior during the day. Important negative historical features might include the lack of REM sleep-related phenomena. Overnight sleep is also usually undisturbed by arousals or excessive movement. It is recognized that mood disorders may be particularly common in idiopathic hypersomnolence although it is not clear whether they are simply a consequence of the sleep disorder [10].

Although not a symptom routinely presented to neurologists, difficulty with morning waking is not uncommon and can lead to significant problems either with education or maintaining employment. If the sleep history indicates that the most likely cause is an abnormally late time of nocturnal sleep onset, the possibility of delayed sleep phase syndrome should be considered. This primarily affects adolescents and is often assumed simply to reflect socio-behavioral factors. However, although bad habits may worsen the situation, it is often a defined disorder of circadian timing such that subjects are "hard wired" to sleep and rise later than average, acting as extreme "night owls" [11]. The diagnosis, if suspected, can be deduced from the history and subsequently supported by investigations.

## **Insomnia**

Chronic insomnia either at sleep onset or through the night is undoubtedly common and most often reflects a combination of psychological and

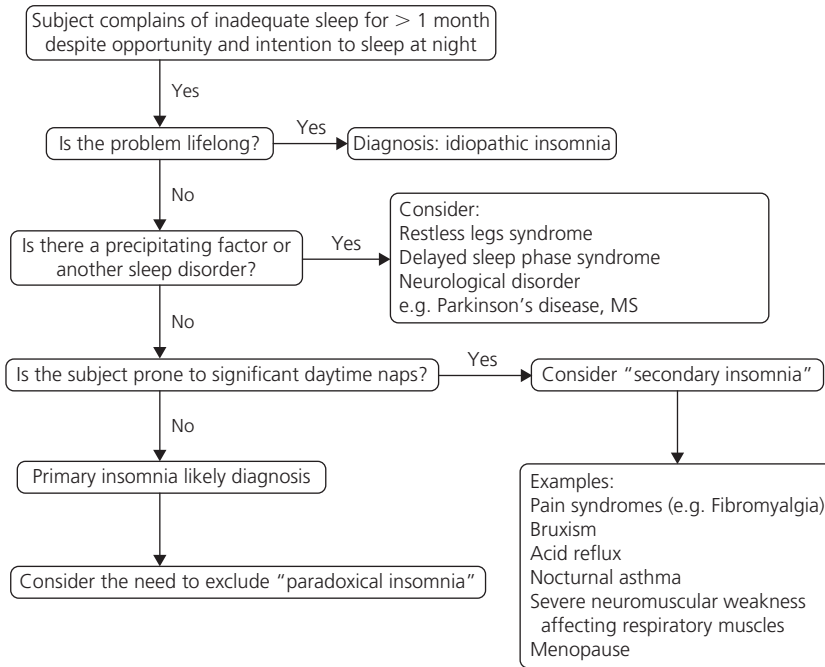
poorly defined constitutional factors. Although a patient's history might indicate severe symptoms, it should be noted that a minority will have so-called "paradoxical insomnia" and will actually sleep fairly well when objectively investigated.

Many chronic insomniacs are able to identify a significant event or lifestyle change that seemed to trigger their sleep disturbance. Despite seemingly severe symptoms of poor nocturnal sleep and reported lethargy, most primary insomniacs are unable to nap during the day. The diagnosis of primary insomnia should therefore be questioned and secondary causes sought in the presence of significant daytime somnolence. This is particularly relevant to neurological populations as insomnia symptoms are common and frequently adversely affect long-term conditions such as epilepsy.

One of the commonest and most under-recognized contributors to delayed sleep onset, sleep fragmentation and, indeed, daytime somnolence is restless legs syndrome (RLS) and associated periodic limb movement disorder (PLMD) (chapter 8). Restless legs syndrome is defined solely from a positive history [12]. There should be restlessness, usually, but not always, in the lower limbs, most often associated with ill-defined sensory symptoms that worsen in the late evening. Symptoms are triggered by rest or immobility and eased, at least temporarily, by movement or rubbing the affected limb or limbs. Associated involuntary jerks can be significant and intrude during wakefulness or light sleep, often adversely affecting sleep quality and causing daytime somnolence. The condition may not be suspected if the upper limbs are predominantly involved or if the symptoms are mistakenly attributed to arthritis or poor circulation, for example. In patients with underlying neuropathies, radiculopathies, or demyelinating disease, restless legs syndrome may be secondary to the primary diagnosis and should not be overlooked. Particularly in younger patients, a positive family history is common and should be actively sought from the history.

Discrete or identifiable brain pathology rarely leads to insomnia as an isolated phenomenon. However, it is relatively common both in neurodegenerative diseases and inflammatory disorders such as multiple sclerosis in the context of more obvious physical neuro-disability [13]. Furthermore, insomnia can also be an apparent direct consequence of head injuries or strokes, particularly those producing subcortical pathology and potentially involving the paramedian thalamic region [14]. Insomnia and severely disturbed sleep are also increasingly recognized accompanying features of limbic encephalitis, a rare disorder in which fluctuating confusion, seizures, and autonomic symptomatology usually predominate [15]. Finally, delayed sleep phase syndrome sometimes presents as insomnia although, unlike the typical case of primary





**Figure 1.1** This algorithm outlines a diagnostic approach to some of the common causes of primary and secondary insomnia that might present to neurologists.

insomnia, by definition, there are also major problems in waking at a conventional hour.

A simple algorithm to assess insomnia presenting to a neurologist is shown in figure 1.1.

## Nocturnal disturbances

Neurologists are frequently asked to assess patients with abnormal nocturnal behaviors or experiences, often with the query, implicit or explicit, as to whether there is an epileptic explanation. Distinguishing parasomnias from epileptic or psychiatric phenomena can clearly be difficult, especially given the practical issues of investigating nocturnal symptoms that are invariably intermittent (see chapter 16). However, a full history supported by spouses and family members together with a detailed background knowledge of parasomnias and their spectrum usually allow for a confident diagnosis.

Sleep-wake transition disorders are poorly studied but often alarming phenomena that may require reassurance if not treatment. They are relatively easy to recognize from the history. Most people are familiar with

an occasional and slightly unpleasant sensation of sudden falling through space at the point of sleep onset. In sleep-wake transition disorders this phenomenon is amplified, more frequent, and often accompanied by a variety of unusual and disturbing sensory or experiential symptoms such as loud auditory or intense visual stimuli. At the more severe end of the spectrum, the so-called “exploding head syndrome” has been described [16]. If frequent or recurrent, significant insomnia at sleep onset and through the night may result.

Parasomnias arising from non-REM sleep are not rare in young adults and probably affect around 1%. They usually reflect incomplete and abnormal arousals from deep non-REM or slow-wave sleep that can lead to a variety of complex and occasionally disturbing nocturnal behaviors. The events themselves usually have relatively little impact on daytime functioning or levels of sleepiness. For a confident diagnosis, it is important to ask about sleep-related phenomena in early childhood as the majority will have a positive history for night terrors, confusional arousals, sleep walking, or all three. Given the likely genetic component to non-REM parasomnias, a family history of nocturnal disturbances, including sleep talking, can also be insightful. In adults, a frequency of one or two events a month is typical, often with identifiable precipitants. These include sleep deprivation, alcohol intake before bed, or sleeping in an unfamiliar or uncomfortable environment. Coinciding with the first period of deep non-REM sleep, the nocturnal disturbance will generally occur within an hour or two of sleep onset and will rarely recur through the night. Subsequent recollection of the event by the subject is at best hazy although agitated events may produce vague memories of nonspecific threats or frightening situations. Detailed or bizarre dream narratives are rare. Events can be prolonged and the subject may appear superficially awake, responding in a limited way to questions and commands. Relatively complex motor tasks such as eating, performing housework and driving are certainly possible.

Distinguishing adult non-REM parasomnias from nocturnal complex partial seizures can be difficult as both may produce complicated behaviors and confusion (see chapter 16). Epileptic episodes are often of frontal lobe origin and can occur several or many times a night from any sleep stage, except REM sleep. If detailed descriptions or, ideally, video clips of several events demonstrate strictly stereotyped episodes, especially with fixed or dystonic limb posturing, a diagnosis of epilepsy is likely. Alternatively, if episodes are long-lasting with an indistinct termination or if they appear to wax and wane, a parasomnia is favored. Strongly expressed emotions or leaving the bed are not particularly discriminatory features.

In a neurological setting, it is commoner to see parasomnias arising from REM sleep, particularly in the context of parkinsonian neurodegenerative

disease. In particular, REM sleep behavior disorder (RBD) typically affects men in late middle age, often many years in advance of any motor or, indeed, cognitive symptomology [17]. The nocturnal disturbances are usually of more concern to the bed partner who may incur injuries from violent dream enactment. The episodes themselves are generally more frequent and prolonged at the end of the night when REM sleep is more prevalent. Movements are often associated with vocalisation and tend to be defensive, brief and undirected, typically involving the upper limbs with eyes generally closed. The subject is usually fairly easy to arouse and will often recall a vivid dream, perhaps involving previous acquaintances or occupations. In certain conditions such as multiple system atrophy and narcolepsy, REM sleep behavior disorder seems to affect females equally [18]. Moreover, in narcolepsy, the dreams and movements may be relatively banal and probably reflect differing underlying pathogenetic mechanisms to those seen in parkinsonism.

The generally restless sleeper can be difficult to diagnose from history alone even if detailed witnessed accounts and videos are available. Periodic limb movement disorder can exist in the absence of restless legs syndrome and is relatively common. Persistent rocking or stereotyped rolling movements involving virtually any body part may reflect a so-called rhythmic movement disorder. This often evolves from childhood “head banging” at sleep onset although can occur in any sleep stage, even REM sleep, in adults [19]. As with many parasomnias, the bed partner is usually the main complainant.

## Conclusions

As within many areas of neurology, a detailed and directed history is paramount when trying to diagnose sleep disorders. The need for a full 24-hour sleep-wake history should be emphasized, corroborated where possible by observers. At the very least, a good history usually provides a credible differential diagnosis which investigations may subsequently further refine. However, if significant diagnostic doubt remains after obtaining a full sleep history, it is relatively rare for sleep investigations to fully elucidate the problem. Furthermore, given the expense and patchy distribution of specialist sleep centers, the sleep history assumes particular diagnostic importance.

Disordered sleep is undoubtedly prevalent in neurological disease and may exacerbate underlying conditions such as migraine and epilepsy. Aside from their direct deleterious effects on daily and nightly functioning, there is therefore ample justification for taking sleep-related symptoms seriously in a neurological setting.

**Key points**

- The patient history is the single most important diagnostic tool in neurological sleep medicine.
- In neurological patients, it can sometimes be difficult to determine whether a sleep-wake symptom is due to an underlying neurological disorder, its treatment or a coexisting primary sleep disorder.
- Excessive daytime sleepiness is not uncommon, and may easily be missed or mistaken for fatigue.
- Additional symptoms not directly related to the sleep-wake cycle may be crucial for the diagnosis (e.g. cataplexy in the case of narcolepsy).
- Sleep onset or sleep maintenance insomnia can reflect an idiopathic or primary phenomenon but is more often secondary to a variety of disorders, including other primary sleep disorders (e.g. restless legs syndrome), psychiatric (e.g. depression) or neurological disease (e.g. multiple sclerosis, neurodegenerative diseases or stroke).
- A knowledge of the typical pattern and spectrum of the various parasomnias normally allows a confident history from history alone and helps exclude epilepsy as a diagnosis.

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## CHAPTER 2

# Polysomnography: indications, interpretation, and pitfalls

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### What is polysomnography?

Electroencephalogram (EEG) monitoring in sleep was carried out as long ago as 1937 [1], but it was only after the discovery of rapid eye movement (REM) sleep in 1953 that this type of recording was combined with other physiological measurements [2]. Polysomnography is the simultaneous acquisition and analysis of data used to assess the sleep state and stage together with a variety of physiological measurements. The latter may include monitoring of respiration, heart rate, leg movements, body position, oesophageal pH, together with video and audio monitoring. Polysomnography should be distinguished from polygraphy in which a range of physiological measurements are obtained, but without formal sleep staging. For example, in multichannel respiratory sleep studies, details of airflow, thoracic and abdominal movement, oxygen saturation and heart rate are obtained but without direct assessment of the sleep-wake state.

### Practical aspects

It is difficult to undertake polysomnography at a subject's home so sleep needs to occur in an unfamiliar environment. The associated anxiety that this generates may distort the findings (so-called "first night effect") [3]. Many centers routinely record over two nights to offset this effect, especially in complex patients. Polysomnography is also dependent on skilled technical expertise and is more expensive than simpler automated studies. It does however enable changes in sleep to be correlated with simultaneous changes in other physiological indices.

The key parameters are recorded by the electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG) through electrodes

fitted to the skin. The signals are filtered and amplified before being stored and displayed by computer [4].

### **Electroencephalogram recording**

The scalp EEG reflects the synaptic activity particularly of parietal cells in the underlying cerebral cortex. These are radially orientated and the electrical field that they generate creates a potential difference between two points on the scalp from which recordings can be made. Although the EEG continuously and noninvasively monitors cortical activity, it is dependent on electrode location and will only produce data from limited locations. The 10–20 montage [5] is rarely employed for polysomnography although it can be essential if information about a localized lesion, such as the source of focal epilepsy, is important. Typically, a limited number of derivations is used. Recent guidelines advocate to record over frontal (e.g. F4-A1), central (e.g. C4-M1), and occipital (e.g. O2-M1) areas.

In non-rapid eye movement (non-REM) sleep the widespread projections of thalamocortical fibers cause synchronized waves of depolarization and hyperpolarization, which are readily detectable at the scalp surface. There may however be local variations in cortical activity. The site of maximum activity of delta waves, for instance, drifts forwards from the occipital towards the frontal cortex during the night.

### **Electro-oculogram recording**

The potential difference between the cornea and the retina acts as an electrical dipole. Movement of the eye generates an electrical current, which can be detected by electrodes placed one centimeter above the outer canthus of the right eye (ROC) and one centimeter below the outer canthus of the left eye (LOC). Slow rolling eye movements occur at the onset of sleep and rapid eye movements, by definition, are characteristic of REM sleep.

### **Electromyogram recording**

This is usually recorded by an electrode under the chin (submental) or on the chin. Other sites, particularly over the anterior tibial muscle, are used to detect activity in specific sleep disorders such as the periodic limb movement disorder. Changes in sustained muscle activity (tone) and the presence of intermittent (phasic) muscle activity are used to assess the presence and stage of sleep.

## **Sleep staging**

The conventional criteria for staging of sleep were published as long ago as 1968 by Rechtschaffen and Kales [6]. They characterize the stage

which predominates during a 30-second epoch. As a result, they only poorly reflect the dynamic nature of sleep and can fail to evaluate rapid fluctuations between sleep stages and states of wakefulness or transitional forms of each of these. These criteria have been validated in healthy young adults but not in most other situations. In practice, there can be difficulty applying the criteria precisely in the presence of many sleep disorders. Computerized analysis of continuous trends in frequency and amplitude of the wave forms are likely to be refined over the next few years.

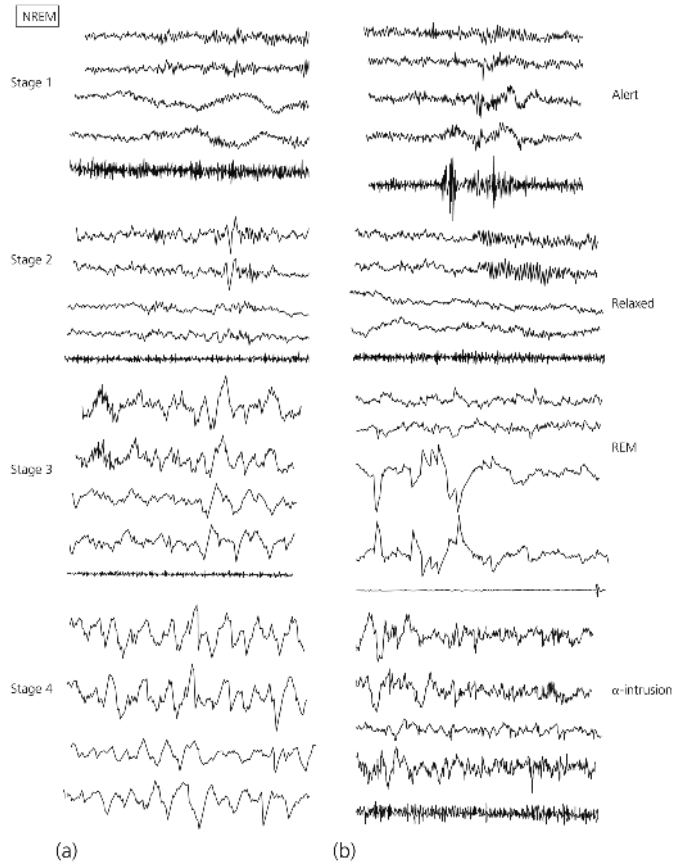
Wakefulness, non-REM sleep and REM sleep can be distinguished by the combinations of their EEG, EOG, and EMG features (figure 2.1). The EEG rhythms are classified primarily by their frequency, but also by their amplitude (table 2.1). The frequency of the EEG slows as sleep is entered with a loss of alpha, and increase in theta and delta waves. Stage 1 non-REM sleep is a transitional state between sleep and wakefulness. Stage 2 is characterized by sleep spindles and K-complexes which are probably sleep-maintaining mechanisms and which appear in response to either internal or external stimuli. In stages 3 and 4 non-REM sleep there is more extensive thalamocortical synchronization with an increase in delta wave activity.

The traditional parameters for sleep staging have recently been updated although the recommendations are yet to be universally accepted or widely used. The new guidelines include more formal definitions of the Rechtschaffen and Kales stages, including the transitions between stages [7]. A more extensive scalp montage is suggested. Stages 3 and 4 are combined into a single stage, N3. Finally, associated events such as apneas, hypopneas and (periodic) limb movements are defined in detail.

The EEG of REM sleep is similar to that of relaxed wakefulness with a wide range of frequencies and low and irregular amplitude waves. The EEG appears to be "desynchronized" but there may be sawtooth waves which precede the rapid eye movements. Skeletal muscles are actively inhibited at the level of the anterior horn cell and this is detected by the absence of any submental EMG signal. There may, however, be occasional phasic muscle twitches. The EOG electrode readily detects the rapid eye movements in this state of sleep.

The instability of normal sleep and arousals due to sleep disorders are poorly recognized by the conventional fixed scoring criteria. As a result, the concept of micro-arousals has been developed, characterized by episodes of increasing EEG frequency lasting at least 3 seconds and following at least 10 seconds of stable sleep [8]. Arousals are a feature of normal sleep and become more frequent with age. Within an otherwise stable phase of sleep, instability can also be detected during which periods of





**Figure 2.1** The EEG, EMG, and EOG appearances. (a) Stage 1 non-REM sleep: high-frequency EEG activity with slow rolling eye movements. Stage 2 non-REM: K-complex with spindles. Stage 3 non-REM: delta waves present in EEG for 20–50% of tracing and conducted to the EOG tracings, less chin EMG activity than in stages 1 and 2 non-REM. Stage 4 non-REM: the EEG shows slow high-amplitude delta waves throughout (or at least 50%) with no chin EMG activity. (b) Alert wakefulness: high-frequency EEG recording with eye movements and considerable chin EMG activity. Relaxed wakefulness: conspicuous alpha rhythm (8–13 Hz) on EEG tracing and chin EMG activity present. REM sleep: irregular mixed frequency EEG with frequent eye movements and absence of chin EMG activity. Alpha intrusion into stage 3 non-REM: alpha waves, superimposed on delta waves in EEG tracing and conducted to EOG recordings. EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; NREM, non-rapid eye movement; REM, rapid eye movement.

partial arousal alternate with times of more stable sleep. This is known as the cyclic alternating pattern (CAP) [9] and can be identified from the EEG by complex computerized analysis. However, its role in clinical practice for detecting unstable sleep remains controversial. Subcortical (autonomic)

**Table 2.1** Electroencephalogram features in sleep and wakefulness

Waveform	Frequency or duration	Amplitude, $\mu$ V	Main sleep-wake state and stage
Beta	>13 Hz	10–20	Alert wakefulness, stage 1 NREM, REM
Alpha	8–13 Hz	20–50	Relaxed wakefulness
Theta	4–8 Hz	10–30	Wakefulness, stage 1 NREM
Delta	0.504 Hz	>75	Stages 2, 3, and 4 NREM
Vertex sharp waves	0.05–10.2 s	30–200	Stage 1 NREM
K-complexes	1 Hz, >0.5 s	>75	Stage 2 NREM
Sleep spindles	12–16 Hz, 0.5 s	20–40	Stage 2 NREM
Sawtooth waves	2–5 Hz, 0.25 s	20–100	REM

NREM, non-rapid eye movement; REM, rapid eye movement.

arousals can also be identified from changes in heart rhythm and blood pressure, which are often accompanied by alterations in respiratory frequency, movements of the limbs and facial muscles, or gross body movements. Autonomic arousals may occur without any overt surface EEG changes.

Of particular interest to physicians involved in the assessment of sleep-related breathing disorders, pressure gauges to assess thoracic and abdominal expansion are useful in discriminating obstructive from central apneas. Nasal airflow and snoring are also routinely recorded.

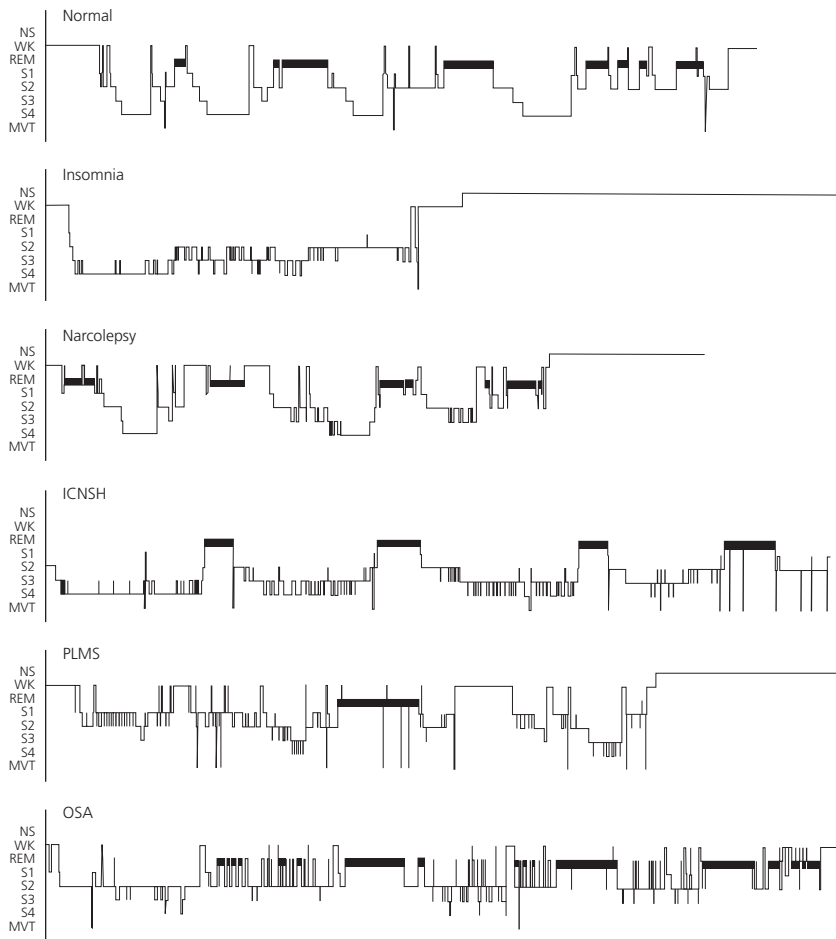
The data from polysomnograph recordings are often summarized in the form of a hypnogram (for examples, see figure 2.2). This shows the distribution of sleep stages and arousals through a night of recording and can be a useful aid, especially when explaining sleep study data to patients.

## Indications

### Excessive daytime sleepiness

The cause of excessive daytime sleepiness (EDS) is often multifactorial and polysomnography may be required in addition to a careful history and sleep diary to assess the relative contributions from several potential sources. These include discrete sleep disorders, sleep deprivation, and circadian rhythm-related problems such as shift work and time zone changes.

Polysomnography is however not generally required if EDS is associated with snoring and witnessed apneas, in the absence of features of any other primary sleep disorder. It is usually sufficient to carry out a respiratory sleep study confined to simple oximetry, measuring oxygen



**Figure 2.2** Hypnograms showing differences between (from top to bottom): normal subject (despite fragmented REM sleep and several brief arousals); insomnia (prolonged period awake at the end of the night); narcolepsy (sleep-onset REM and frequent sleep-stage shifts); idiopathic hypersomnia (prolonged episodes of stage 3 and 4 non-REM sleep); periodic limb movement syndrome (frequent arousals early in the night with difficulty in establishing stages 3 and 4 non-REM sleep); and OSAs (frequent arousals and lack of stages 3 and 4 non-REM sleep). MVT, movement artefact; NREM, non-rapid eye movement; NS, no signal; OSA, obstructive sleep apnea; REM, rapid eye movement; S1–4, stages 1–4 NREM sleep; WK, wakefulness.

saturation and heart rate. This is often combined with other respiratory recordings, particularly thoracic and abdominal movement and airflow. These additional monitors enable obstructive to be distinguished from central sleep apneas.

Information from polysomnography is useful in situations in which knowledge of the sleep architecture helps to define the clinical problem.

For example, the presence or absence of sleep-onset REM sleep, the frequency and causes of arousals from sleep such as periodic limb movements, and the nature of abnormal physical activities during sleep may be accurately determined. The severity of EDS is assessed by daytime tests, notably the Multiple Sleep Latency Test (MSLT), which is discussed in detail in chapter 3 [10].

Some examples of specific indications for polysomnography in the investigation of EDS are discussed below. They are further detailed in several other chapters.

### **Narcolepsy**

In narcolepsy, although polysomnography is primarily used to rule out other causes of EDS, there are some features that are typical if not diagnostic. The sleep latency is usually less than 5–10 minutes, but there is little or no increase in the total time asleep during the night [11] (figure 2.2). Sleep-onset REM sleep is defined as the appearance of REM sleep within 20 minutes of the onset of nocturnal sleep and occurs in around 50% of patients. There may be an increase in the duration of stage 1 non-REM sleep with shortened stages 3 and 4 together with considerable disruption of sleep with frequent awakenings. This is a feature particularly of older subjects with narcolepsy. Periodic limb movements may also be seen during sleep and, unlike other conditions, these often occur during REM rather than non-REM sleep. Phasic and tonic muscle activity may also be seen in REM sleep in narcoleptics and frank REM sleep behavior disorder (RBD) may be observed. This is characterized by unpleasant dreams with an aggressive or vigorous content that are physically enacted. In narcolepsy, this phenomenon affects males and females equally and there is probably a tendency for the behaviors to be less vigorous than in other causes of RBD.

### **Idiopathic hypersomnia**

Idiopathic hypersomnia is characterized by a short sleep latency with long total sleep time, high sleep efficiency, and few arousals from sleep. The duration of the non-REM sleep episodes tends not to shorten later in the night as in normal subjects. The total duration of stages 3 and 4 non-REM sleep may be increased in contrast with narcolepsy and there is no sleep-onset REM sleep.

### **Myotonic dystrophy**

As in other significant neuromuscular disease, polysomnography may reveal central or occasionally obstructive sleep apneas which may be partly responsible for EDS. Periodic limb movements may also be present.

The sleep latency is typically shortened and sleep-onset REM sleep is common.

### **Parkinson's disease**

There are many potential causes of EDS in Parkinson's disease. Pathology in the sleep-wake controlling mechanisms caused by the disease itself tends to reduce stages 3 and 4 non-REM sleep and REM sleep although sleep-onset REM sleep is common. Sleep efficiency is substantially reduced, particularly when the disease is extensive. The disturbed sleep profile in severe cases can resemble that seen in narcolepsy.

### **Insomnia**

Polysomnography is not usually required to investigate chronic insomnia unless there are suspicions regarding secondary causes or if there is likely sleep state misperception (paradoxical insomnia) rather than true insomnia. This latter phenomenon is difficult to distinguish clinically from true insomnia (figure 2.2). In primary insomnia, polysomnography may simply show prolonged episodes of wakefulness during the night. If there are associated psychiatric problems, such as depression, there may not only be a short total sleep time but REM sleep latency is decreased, REM sleep duration increased, and stages 3 and 4 non-REM sleep reduced.

Polysomnography may also be of value in confirming the presence and severity of the following conditions which may contribute to insomnia.

### **Restless legs syndrome and periodic limb movements during sleep**

Restless legs syndrome (RLS) is the cause of insomnia in around 10% of patients referred to specialist sleep centers, and while its diagnosis may often be obvious clinically, polysomnography can help to consolidate the diagnosis by revealing significantly associated PLMs. The anterior tibial EMG reveals repetitive muscle activity of 0.5 to 5 seconds duration with an intermovement interval of 5 to 90 seconds in a sequence of four or more movements [11]. Video recordings also show the type and frequency of movements, although these may be obscured by the bed clothes, particularly if movements are of small amplitude. These movements are most frequent in stages 1 and 2 non-REM sleep and usually absent in REM sleep, except in narcolepsy. If they occur during wakefulness at night they may prevent sleep onset. Their frequency can be recorded as the periodic limb movement index per hour with a normal value of less than 5 per hour in young adults.

### **Sleep state misperception**

In this condition, the patient complains of difficulty in sleeping at night but objective tests show that the sleep latency and poor sleep efficiency is exaggerated. Polysomnography characteristically shows a normal sleep duration, sleep latency, and sleep architecture with a normal number of arousals and no evidence for any other primary sleep disorder.

### **Fibromyalgia and chronic fatigue syndrome**

In these conditions polysomnography typically shows a prolonged sleep latency, increased number of arousals from sleep, with reduced stages 3 and 4 non-REM sleep duration, reduced duration of REM sleep, and so-called “alpha intrusion” into deep non-REM stages. The extent of alpha activity may related to the severity of musculoskeletal discomfort and the sensation of sleeping lightly at night.

### **Dementia**

Polysomnography is only required if the sleep disorder becomes troublesome and a separate condition is suspected. In most dementias, polysomnography characteristically shows a marked reduction in sleep efficiency and frequent and prolonged awakenings. Both stages 3 and 4 non-REM sleep are shortened and there are fewer sleep spindles and K-complexes than normal. REM sleep latency is increased and periodic limb movements during sleep are common. Central and obstructive sleep apneas may develop together with Cheyne-Stokes respiration.

### **Motor disorders of sleep**

Polysomnography is not required for many of these conditions, such as sleep talking or sleep bruxism, but should be considered when:

- 1** The diagnosis is unclear;
- 2** There are atypical features, such as appearance of sleep walking for the first time in an adult;
- 3** The possibility exists that episodes may be triggered by another sleep disorder, such as obstructive sleep apneas;
- 4** The activities are potentially dangerous to the patient or others;
- 5** The events fail to respond to initial treatment.

### **Non-REM sleep arousal disorders**

These include confusional arousals, sleep walking, and sleep terrors. If events are captured, the video recording usually reveals a characteristic sudden onset and gradual ending of these activities. The patient usually

appears frightened in sleep terrors whether these occur in childhood or adult life. All these episodes occur particularly within the first third of the night and typically around 1.5 hours after the onset of sleep [12]. Polysomnography shows that they usually arise from stages 3 and 4 of non-REM sleep. Even in the absence of overt behavioral changes, there may be frequent sudden arousals from stages 3 and 4 non-REM sleep. The events may be preceded by hypersynchronous delta activity which presumably reflects a failed attempt of the cerebral cortex to maintain sleep in the face of an arousing stimulus. Specific causes or triggers for the arousal disorder, such as obstructive or central sleep apneas, or periodic limb movements, may also be detected.

### **REM sleep behavior disorder**

In REM sleep behavior disorder (RBD) the video recording usually reveals either brief twitches, particularly of the hands or face, or more directed movements, such as pointing and shouting at a perceived aggressor. Running or kicking movements are common and occasionally the subject may dive or jump out of bed. The polysomnograph shows normal sleep architecture but muscle tone is maintained in REM sleep, often with profound phasic muscle twitches. This activity is best seen in the submental EMG but is readily seen in other muscle groups. Attempts have been made to quantify the phenomena [13] but no criteria have been generally agreed. Sufficient abnormalities are usually seen during the first night of polysomnography to confirm the diagnosis [14]. Periodic limb movements may also occur both in non-REM and occasionally in REM sleep.

### **Epilepsy**

Several forms of partial and generalized epilepsy occur during sleep. The frontal lobe epilepsies are the most closely associated. If events are captured, polysomnography usually shows brief posturing at the onset of the episode followed by stereotyped movements affecting one or more limbs and axial muscles. The movements may be frenetic and the subject may leave the bed. The EEG shows a movement artefact at the onset of the episode but no specific epileptic features either during or after the event.

In other types of epilepsy, high amplitude spikes or waves may be detected between or during seizures, particularly in non-REM sleep [15]. A full montage EEG is preferable to standard polysomnography montage, if localized epileptic discharges being sought [16]. Polysomnography is also useful to distinguish epileptic from nonepileptic behaviors during sleep although clearly events need to be captured.

## Pitfalls in interpretation

Polysomnography, like all other investigations, has its limitations and should be interpreted in the context of a full history. Particular care should be taken not to either misinterpret polysomnographic findings or overinterpret them. Common pitfalls are discussed further.

### Artefacts

These may arise from the recording system or have a physiological cause. Difficulties in interpreting the results may be due to power failure, electrical interference, amplifier defects, broken or loose electrodes, poor contact or problems with the reference electrode. Physiological factors include sweating, prominent electrocardiogram (ECG) signals, and movement artefact which be due to arousals from sleep or to more localized activities such as jaw and tongue movements and limb tremor. Video analysis may also be limited if the patient moves out of the range of the camera, and audio recordings may be obscured by noise if the patient leaves the television or radio on during the night.

### Normal variants

There is a wide range of normal activities during sleep and some usual EEG patterns may be mistakenly taken as representative of a sleep disorder rather than a normal variant. There is also considerable interobserver variation in the analysis of polysomnographic recordings [17] although “manually” scored recordings are more accurate and preferred to the computerized reporting systems that have been developed.

### Inadequate sleep

The patient may sleep poorly during the night of the polysomnography and the stage of sleep in which the event was most likely to occur may be absent or curtailed. Nocturnal epilepsy, for example, arises most frequently from stage 2 non-REM sleep and the epileptic features may not be apparent if this is shortened or fragmented, for instance by obstructive sleep apneas. The diagnosis of REM sleep behavior disorder requires the appearance of REM sleep during the night. If there is none, clearly few conclusions can be drawn.

### Prior sleep history

The sleep history on the nights preceding polysomnography and for up to 2 weeks beforehand may influence the interpretation of the study. Sleep deprivation promotes a short sleep latency, increases stages 3 and 4 non-REM sleep, and often increases REM sleep. These features may mimic disorders such as narcolepsy or idiopathic hypersomnia.



### **Other medical disorders**

The interpretation of polysomnography may be difficult if there is more than one sleep disorder or a separate medical condition. The diagnosis of narcolepsy for instance may be obscured by frequent obstructive sleep apneas until these are treated. Sleep apneas themselves are characterized by arousals which cause anterior tibial EMG activity in a pattern similar to periodic limb movements.

### **Drug effects**

Many drugs affect sleep and hinder the accurate interpretation of polysomnography. Most antidepressants inhibit and delay REM sleep, potentially masking the characteristic features of narcolepsy if prescribed either for depression or for suspected cataplexy [18]. Conversely, sedative hypnotics or opiates can worsen obstructive sleep apneas and give a false impression of their severity. Benzodiazepines and alcohol, in particular, also inhibit REM sleep and increase the proportion of light stage 2 non-REM sleep, perhaps explaining the generally unrefreshing nature of nocturnal sleep after these agents.

### **Referral to a specialist sleep center**

Referral to a specialist center may be appropriate either for a clinical opinion and advice about further investigation or specifically for polysomnography if this is not otherwise available. The referring physician or neurologist should have an understanding of the possibilities and limitations of the investigations. It is important to differentiate situations in which it is relatively important to establish a definite diagnosis and those in which empirical treatment can appropriately be given without polysomnography. In general, it is more imperative to establish the nature of the diagnosis when:

- 1 The condition is likely to be life-long, e.g. narcolepsy, idiopathic hypersomnia;
- 2 There are atypical features such as the apparently sudden onset of sleep "walking" in adult life;
- 3 There is failure to respond to initial treatment;
- 4 The activities during sleep are potentially dangerous, including REM sleep behavior disorder;
- 5 There may be more than one sleep disorder contributing to the symptoms (e.g. the common combination of obstructive sleep apneas and periodic limb movements during sleep) and their relative importance is uncertain.

**Key points**

- Polysomnography enables information about the sleep state and other physiological parameters to be acquired simultaneously.
- Continuous EEG, EOG, and EMG recordings are required to score sleep into distinct stages.
- Interpretation requires an understanding of technical issues, prior sleep history, and assessment of other medical disorders and medication.
- Polysomnography is not usually required to evaluate obstructive or central sleep apneas, but can be of value in narcolepsy and other organic neurological disorders causing sleepiness, especially if more than one disorder exists.
- Polysomnography is only indicated in insomnia when specific secondary causes are suspected such as periodic limb movements in sleep.
- Polysomnography can help to distinguish non-REM sleep arousal disorders from REM sleep motor disorders and epilepsy. It is indicated particularly if there are atypical features or the activities are potentially dangerous. It can also be useful in treatment failures, especially if there exists a combination of sleep disorders in the same patient.

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## CHAPTER 3

# Daytime tests for sleepiness: indications, interpretation, and pitfalls

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### Introduction

This chapter focuses on the two most widely used laboratory-based objective tests for the measurement of sleepiness, the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT). The MSLT is currently mainly used for diagnostic purposes, and the MWT for the quantification of sleepiness.

### What is sleepiness?

During daytime it is considered normal to be able to stay awake, even in monotonous situations. In this ideal view sleepiness should only occur just before the habitual start of nocturnal sleep. Excessive sleepiness can accordingly be defined as sleepiness and/or sleep occurring during daytime in a situation when an individual would be expected to stay fully awake. At any point in time, daytime sleepiness affects approximately 5–15% of the general population in Western countries [1]. It is important to realize that excessive sleepiness is a symptom and not a diagnosis. It is not even necessarily a symptom of a sleep disorder, as external factors leading to sleep deprivation and/or disruption may, for example, induce sleepiness that is perceived as “excessive.”

Daytime sleepiness can present in two qualitatively different ways:

- 1 An increased amount of sleep over the 24-hour period, for which the word “hypersomnia” was originally coined. It is characterized by an extended nocturnal sleep period and a complaint of daytime sleepiness;
- 2 The inability to stay awake during daytime, usually without an increased amount of sleep over the 24-hour period, for which the term “excessive daytime sleepiness” or EDS was originally used.

Unfortunately, there is a tendency to use these terms interchangeably, obscuring a possible essential difference in pathophysiology. The correct use may provide important clues for a specific diagnosis, and may, to a certain extent, predict the result of the performed MSLT or MWT [2,3].

### **Testing sleepiness**

An ideal objective test for daytime sleepiness should not only have diagnostic value, but should also quantify the severity of sleepiness and be easy to apply. Not surprisingly, there is no ideal test. The currently available tests (MSLT and MWT) are troublesome in that they may leave diagnostic uncertainty while they do not reliably predict problems that patients experience in daily life, nor do they reliably predict the risk for accidents [2]. The most plausible explanation for these limitations is that “sleepiness” is essentially subjective in nature and therefore too complex to be represented by sleep latency alone. Nevertheless, both tests have a role in the evaluation of sleepiness.

### **Multiple Sleep Latency Test**

The MSLT was introduced in 1977; it was standardized and generally accepted in 1986 [5,6]. Separate clinical and research protocols were originally described. The clinical variant allowed the occurrence of short sleep episodes to permit REM sleep to emerge, whereas the research protocol was designed to limit the occurrence of sleep by waking up the subject immediately after sleep onset to prevent any recovery of sleepiness.

#### **Clinical protocol**

The clinical version is performed as follows: subjects with electrodes attached for standard sleep recording are requested to try to fall asleep in a quiet and dimmed bedroom. Four to five sessions – sleep latency tests – are performed throughout the day with 2-hour intervals. The subject is asked to stay in bed for 20 minutes when no sleep occurs. When the subject falls asleep the duration is altered to ensure recording for 15 minutes after the onset of sleep. Sleep onset is defined as the first epoch of any sleep stage, including stage 1. The sleep onset latency is the time in half minutes from “lights-out” until the criterion of sleep onset is met, or is noted as 20 minutes when sleep did not occur. The final score is the average of values of the separate sleep latency tests over the day. The MSLT must be performed immediately after polysomnography recorded during the individual’s major sleep episode. For a detailed description see table 3.1 [4].

**Table 3.1** The current guideline from the American Academy of Sleep Medicine for the performance of the MSLT [4]

Recommendations for the MSLT protocol	
1	The MSLT consists of five nap opportunities performed at 2-hour intervals. The initial nap opportunity begins 1.5 to 3 hours after termination of the nocturnal recording. A shorter four-nap test may be performed but this test is not reliable for the diagnosis of narcolepsy unless at least two sleep onset REM periods have occurred.
2	The MSLT must be performed immediately following polysomnography recorded during the individual's major sleep period. The use of MSLT to support a diagnosis of narcolepsy is suspect if TST on the prior night sleep is less than 6 hours. The test should not be performed after a split-night sleep study (combination of diagnostic and therapeutic studies in a single night).
3	Sleep logs may be obtained for 1 week prior to the MSLT to assess sleep-wake schedules.
4	Standardization of test conditions is critical for obtaining valid results. Sleep rooms should be dark and quiet during testing. Room temperature should be set based on the patient's comfort level.
5	Stimulants, stimulant-like medications, and REM suppressing medications should ideally be stopped 2 weeks before MSLT. Use of the patient's other usual medications (e.g. antihypertensives, insulin, etc.) should be thoughtfully planned by the sleep clinician before MSLT testing so that undesired influences by the stimulating or sedating properties of the medications are minimized. Drug screening may be indicated to ensure that sleepiness on the MSLT is not pharmacologically induced. Drug screening is usually performed on the morning of the MSLT but its timing and the circumstances of the testing may be modified by the clinician. Smoking should be stopped at least 30 minutes prior to each nap opportunity. Vigorous physical activity should be avoided during the day and any stimulating activities by the patient should end at least 15 minutes prior to each nap opportunity. The patient must abstain from any caffeinated beverages and avoid unusual exposures to bright sunlight. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the second noon trial.
6	Sleep technologists who perform MSLTs should be experienced in conducting the test.
7	The conventional recording montage for the MSLT includes central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electro-oculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG).
8	Prior to each nap opportunity, the patient should be asked if they need to go to the bathroom or need other adjustments for comfort. Standard instructions for bio-calibrations (i.e. patient calibrations) prior to each nap include: (1) lie quietly with your eyes open for 30 seconds, (2) close both eyes for 30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly 5 times, and (5) clench or grit your teeth tightly together.

**Table 3.1** (Continued)

Recommendations for the MSLT protocol	
9	With each nap opportunity the subject should be instructed as follows: "Please lie quietly, assume a comfortable position, keep your eyes closed and try to fall asleep." The same instructions should be given prior to every test. Immediately after these instructions are given, bedroom lights are turned off, signaling the start of the test. Between naps, the patient should be out of bed and prevented from sleeping. This generally requires continuous observation by a laboratory staff member.
10	Sleep onset for the clinical MSLT is determined by the time from lights out to the first epoch of any stage of sleep, including stage 1 sleep. Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch. The absence of sleep on a nap opportunity is recorded as a sleep latency of 20 minutes. The latency is included in the calculation of mean sleep latency (MSL). In order to assess for the occurrence of REM sleep, in the clinical MSLT the test continues for 15 minutes from after the first epoch of sleep. The duration of 15 minutes is determined by "clock time," and is not determined by a sleep time of 15 minutes. REM latency is taken as the time of the first epoch of sleep to the beginning of the first epoch of REM sleep regardless of the intervening stages of sleep or wakefulness.
11	A nap session is terminated after 20 minutes if sleep does not occur.
12	The MSLT report should include the start and end times of each nap or nap opportunity, latency from lights out to the first epoch of sleep, mean sleep latency (arithmetic mean of all naps or nap opportunities), and number of sleep-onset REM periods (defined as greater than 15 sec of REM sleep in a 30-sec epoch).
13	Events that represent deviation from standard protocol or conditions should be documented by the sleep technologist for review by the interpreting sleep clinician.

## Validation

The capability of the MSLT to measure sleepiness was established by applying the test to a group of healthy volunteers who were deprived of sleep to different degrees [7]. Significant correlations between the severity of deprivation and sleep latency the next day were found. Moreover, there was a significant correlation between subjective sleepiness scales such as the Stanford Sleepiness Scale and sleep latency (SL) on nap opportunities [8]. Test-retest reliability, and inter- and intrarater reliability were all high [9–11]. Hypnotic drugs also produced the expected changes [11]. These findings were so reassuring that it was concluded that sleep latency as assessed during the MSLT represents an objective quantitative score of sleepiness, and studies to obtain normative data in large population-based cohorts were not undertaken. Another consequence was that the MSLT was subsequently used as the main diagnostic test for sleep disorders characterized by EDS and for the quantification of

the severity of sleepiness. Because of the influence of sleep deprivation as assessed previously, it was considered mandatory to precede the MSLT by a night in which the subject slept at least 6 hours, as recorded with polysomnography. Validation studies were largely limited to narcolepsy. It was found that the vast majority of narcoleptic patients were characterized not only by short sleep latency but also by the occurrence of multiple sleep-onset REM periods (SOREMs). However, multiple SOREMs were not exclusively found in narcolepsy but also occasionally in other disorders, particularly obstructive sleep apnea syndrome (OSAS) [11,12]. Test-retest reliability of SOREMs in patients with narcolepsy was found to be high [11].

## **Maintenance of Wakefulness Test**

The usefulness of the MSLT as an objective test to quantify improvement in sleepiness after therapeutic interventions turned out to be disappointing, particularly in narcolepsy [13]. MSLT results usually did not relate clearly to subjectively experienced improvements in sleepiness, for which a “floor effect” was hypothesized: in very sleepy patients improvements were not detected because the test lacked sensitivity to tell severe and moderate sleepiness apart. It was also argued that the test did not reflect normal daily life: patients with EDS try to stay awake instead of to fall asleep, and they also do not spend their time in darkness without alerting factors. A new test dealing with these shortcomings was developed in 1982: the Maintenance of Wakefulness Test (MWT) [14].

## **Clinical protocol**

During the MWT, the subject has to sit up in a chair in a quiet and dimly lit room with the instruction to stay awake, which better reflects the situation in normal daily life. Vocalizations and movements are not allowed. The rest of the procedure is comparable to the MSLT: four or five sessions throughout the day, and the occurrence of sleep is recorded. To increase the sensitivity the recommended duration of each session is increased from 20 to 40 minutes in the recent guideline. For a detailed description see table 3.2 [4].

## **Validation**

The MWT indeed detected treatment effects better than the MSLT, but the correlation with subjective experienced improvements and performance was still only moderate. An exception may be driving performance in untreated OSAS patients [15]. Another problem is the large variation in the way the test is performed in various studies. Test periods are either 20 or 40 minutes, there are either four or five nap opportunities



**Table 3.2** The current guideline from the American Academy of Sleep Medicine for the performance of the MWT [4]

Recommendations for the MWT protocol	
1	The 4-trial MWT 40-minute protocol is recommended. The MWT consists of four trials performed at 2-hour intervals, with the first trial beginning about 1.5 to 3 hours after the patient's usual wake-up time. This usually equates to a first trial starting at 0900 or 1000 hours.
2	Performance of a PSG prior to MWT should be decided by the clinician based on clinical circumstances.
3	Based on the Rand/UCLA Appropriation Method, no consensus was reached regarding the use of sleep logs prior to the MWT; there are instances, based on clinical judgment, when they may be indicated.
4	The room should be maximally insulated from external light. The light source should be positioned slightly behind the subject's head such that it is just out of his/her field of vision, and should deliver an illuminance of 0.10–0.13 lux at the corneal level (a 7.5 W night light can be used, placed 1 foot off the floor and 3 feet laterally removed from the subject's head). Room temperature should be set based on the patient's comfort level. The subject should be seated in bed, with the back and head supported by a bedrest (bolster pillow) such that the neck is not uncomfortably flexed or extended.
5	The use of tobacco, caffeine and other medications by the patient before and during MWT should be addressed and decided upon by the sleep clinician before MWT. Drug screening may be indicated to ensure that sleepiness/wakefulness on the MWT is not influenced by substances other than medically prescribed drugs. Drug screening is usually performed on the morning of the MWT but its timing and the circumstances of the testing may be modified by the clinician. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the second noon trial.
6	Sleep technologists who perform the MWT should be experienced in conducting the test.
7	The conventional recording montage for the MWT includes central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electro-oculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG).
8	Prior to each trial, the patient should be asked if they need to go to the bathroom or need other adjustments for comfort. Standard instructions for bio-calibrations (i.e. patient calibrations) prior to each trial include: (1) sit quietly with your eyes open for 30 seconds, (2) close both eyes for 30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly 5 times, and (5) clench or grit your teeth tightly together.
9	Instructions to the patient consist of the following: "Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light." Patients are not allowed to use extraordinary measures to stay awake such as slapping the face or singing.
10	Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch.
11	Trials are ended after 40 minutes if no sleep occurs, or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep.
12	The following data should be recorded: start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for each trial, and the mean sleep latency (the arithmetic mean of the four trials).
13	Events that represent deviation from standard protocol or conditions should be documented by the sleep technologist for review by the sleep specialist.

and there are different definitions of sleep onset. These differences may profoundly affect the outcome and normal values (see “Normative data” below). The MWT is not used for the diagnosis of a specific sleep disorder, but is used to quantify sleepiness. In narcolepsy data are only from pharmacological trials which usually recruit selected patient groups. Baseline values in these trials show mean SL values below 11 minutes, independent of the 20 or 40-minute protocol and the definition of sleep onset.

## **Normative data**

### **Multiple Sleep Latency Test**

Normative values for the MSLT depend on a variety of small studies with often unclear selection criteria, a lack of population-based studies, as well as unclear protocol details. Moreover, many factors influence the results of the MSLT: age (in adults latency increases with age), sex, number of naps (five naps result in a longer mean sleep latency than four naps), use of psychotropic medication, anxiety, depression, and HLA DQB1\*0602 positivity [11,16,17]. Inadvertent naps in between the scheduled naps of the MSLT do not seem to influence the sleep latency of the scheduled naps significantly [18]. Healthy subjects may increase their sleep latency by trying to stay awake during the test [19]. The degree of physical activity between the tests may substantially influence sleep latency, at least in healthy subjects before and after sleep deprivation [20]. The occurrence of SOREMs is influenced by age, circadian rhythm, and use of certain psychotropic drugs such as tricyclic antidepressants and the majority of selective serotonin reuptake inhibitors (SSRIs) [11,16,17].

The pooled data of all these studies resulted in the following “normal values”: a mean SL of  $10.4 \pm 4.3$  minutes for the 4 SLT protocol and  $11.6 \pm 5.2$  minutes for the 5 SLT variant [4]. Note that the above-mentioned influences were not taken into account, except for one: the subjects were free of psychotropic medication. Due to this large spread the distributions of patients’ and control values overlap substantially. Furthermore, a recent community-based study in over 500 subjects found that a mean  $SL \leq 8$  minutes and  $\geq 2$  SOREMPs (i.e. the diagnostic criteria for narcolepsy) are observed in 5.9% of males and 1.1% of females, confirming findings in some earlier, largely neglected, small studies. None of the included subjects had cataplexy and the majority had an Epworth Sleepiness score  $\leq 10$ . If we assume that these subjects did not suffer from narcolepsy, which is probably the case in view of their low Epworth Sleepiness Scale scores, then this finding has consequences for the interpretation of MSLT results. Of all people with a  $SL < 8$  minutes and  $\geq 2$  SOREMPs, only a very small minority will actually have narcolepsy. Although 6% of all men may not

seem much for a false positive result, this should be compared to common standards for laboratory tests, in which a 2 or 3 standard deviation threshold is often used to delineate abnormality. For a 2 SD threshold, a false positive rate of 2.5% may be expected. Compared to this a value of 6% is appreciably higher. It may well be wondered if such a rate is not too high for a test considered to be the “gold standard” for a particular diagnosis. The extent to which this intriguing fact affects the diagnostic yield of the MSLT for the detection of narcolepsy depends on which proportions of these populations are actually investigated for sleepiness.

### Maintenance of Wakefulness Test

As with the MSLT, there is no large multicenter systematically collected set of normative data nor a large population-based study. An additional complicating factor is that different protocols were used. Normative data calculated from the available literature for the various protocols are [11]:

- 20 minute protocol; four nap opportunities; sleep onset defined by three epochs of stage 1 sleep or one epoch of any other sleep stage:  $18.8 \pm 3.3$  minutes;
- 40 minute protocol; four nap opportunities; sleep onset defined by three epochs of stage 1 sleep or one epoch of any other sleep stage:  $35.2 \pm 7.8$  minute;
- 40 minute protocol; four nap opportunities; sleep onset defined by first epoch of sleep including stage 1:  $30.4 \pm 11.20$  minutes.

The MWT is significantly influenced by psychotropic medications, the prior amount of sleep, physical activity, motivational factors, and age: latency increases with age [4,19–21]. There is a limited impact of inadvertent sleep between the sessions and of the duration of previous nocturnal sleep [18]. Similar to the MSLT there is a large overlap between findings in patients and the normal population. It has been suggested that 8 minutes should be considered as the lower limit of normal (for the 40 minutes; four-nap first epoch variant) [4,11]. This would correspond to a false positive rate of 2.5% in the normal population [4].

### Diagnostic criteria

There have been some changes in the diagnostic criteria between the first (1990) and the second (2005) version of the *International Classification of Sleep Disorders* [2]. For example, a pathological level of sleepiness was first assigned to a mean SL of less than 5 minutes, and later changed to less than 8 minutes. Below, we list the current criteria for the most important sleep disorders characterized by daytime sleepiness.

**Narcolepsy with cataplexy and narcolepsy without cataplexy**

Apart from meeting clinical criteria, a MSLT is mandatory to diagnose narcolepsy without cataplexy [2]. In narcolepsy with (typical) cataplexy, the MSLT is essentially optional, but recommended to confirm the diagnosis, although hypocretin-1 measurement may be sufficient. Criteria for the diagnosis of narcolepsy with and without cataplexy are a mean SL  $\leq 8$  minutes *and*  $\geq 2$  SOREMs. It is important to realize that more than 10% of patients suffering from narcolepsy with cataplexy, and who are hypocretin deficient, may not fulfill these criteria [22].

**Idiopathic hypersomnia**

Besides the required clinical criteria, and criteria to separate idiopathic hypersomnia (IH) with long sleep time variant from IH without long sleep, a MSLT must be part of the diagnostic process [2]. A mean sleep latency of  $< 8$  minutes and  $< 2$  SOREMs is mandatory. Note that this criterion is not evidence based. Particularly for IH with long sleep time there is little evidence that these criteria improve the accuracy of the diagnosis.

**Hypersomnia due to medical condition**

An MSLT is not required for the diagnosis [2]. However, when a MSLT is performed, the mean SL should be  $< 8$  minutes. In neurodegenerative disorders, the EEG may occasionally be difficult to interpret. Comparing signals obtained during nocturnal sleep with those found during MSLT testing may sometimes facilitate the interpretation.

**Parkinson's disease**

The MSLT frequently shows a short SL, and less frequently SOREMs. Correlations with subjective complaints are not consistent, however, and dopaminergic medication may induce the EDS [23,24]. Data on the use of the MWT in Parkinson's disease are scarce. One small study (20 patients in a tertiary care center) showed a high percentage of patients fulfilling criteria for EDS on the MSLT, but with relatively long latencies during MWT testing. The mean SL of the MSLT was 3.1 minutes, for the MWT it was 20.9 minutes (40-minute variant) in patients with a complaint of EDS. Respective values were 10.9 and 33.3 minutes in patients without a complaint of EDS [24].

**Myotonic dystrophy**

The MSLT is frequently abnormal showing a short SL. SOREM occurs relatively frequently, usually in association with complaints of EDS [25].

**Traumatic brain injury**

In a cohort study, 28% of patients with traumatic brain injury had complaints of EDS and 25% showed a mean SL < 5 minutes on MSLT testing, 6 months after the trauma [26].

**Behaviorally induced insufficient sleep syndrome**

A MSLT is not mandatory for the diagnosis [2]. There are few studies; a SL < 8 minutes and SOREM was reported to occur without estimates of its frequency [2].

**Sleep-related breathing disorders**

Neither the MSLT nor the MWT are required for the diagnosis of any sleep-related breathing disorder [2].

**Recommendations for use and interpretation****Clinical shortcomings**

Ideally, a diagnostic test in medicine should be directly related to the pathophysiological process. This is however not the case for the MSLT and MWT. Both use SL as a surrogate marker for sleepiness, but in different predefined circumstances. It is important to realize that the use of SL as a suitable surrogate marker is based on several assumptions. For example, it is assumed that subjectively experienced sleep and sleep as measured by polysomnography correlate well, or are even identical. Or that the SL is only influenced by the degree of sleepiness. However, these assumptions should always be critically assessed. The use of stage 1 as 'sleep' is controversial, and it has been shown that individuals who are "polysomnographically asleep" are not asleep by their own subjective experience [27]. Importantly, sleep onset is not only influenced by sleepiness, but also by motivational and environmental factors. Likewise, the use of sleep latency as a diagnostic measure prevents a distinction between sleep deprivation and a (primary) sleep disorder, which is important to realize as sleep deprivation is not easy to identify because of the large interindividual variation in need for sleep.

Finally, there may be a difference between sleepiness and the ability of the brain to make the transition from wake into sleep. Some subjects may be able to fall asleep very quickly without suffering from EDS while awake. This important point is largely neglected in the literature. In narcolepsy, there may primarily be a "transition disorder," the inability to sustain either the waking or the sleeping state for any length of time [13,28,29].

**Multiple Sleep Latency Test in practice**

The MSLT is, despite the discussed shortcomings, still a valuable test in the diagnosis of hypersomnia and disorders characterized by EDS. It is in fact the only objective test used for the diagnosis of narcolepsy without cataplexy. The test does not stand on its own: it is crucial to interpret the results in any patient in the context of the patient's symptoms and of other tests. Since several percent of the normal population seem to fulfill the criteria of hypersomnia and/or narcolepsy without cataplexy, although they may not have any complaint, the MSLT can never be the sole pillar for such a diagnosis. It is not clear whether the relatively high percentage of abnormal findings in the normal population may be explained by sleep disturbances and/or deprivation; whether a much higher prevalence of sleep disorders characterized by EDS exists than was previously estimated; or whether the MSLT is susceptible to as yet unidentified factors. One should keep in mind that a negative test result may be found in disorders characterized by a need for increased sleep duration, the classical hypersomnias. But even in typical cases of narcolepsy with cataplexy with a proven hypocretin deficiency the MSLT may occasionally be negative. The MSLT has a very limited role as a tool to detect improvement of sleepiness in therapeutic trials, particularly in narcolepsy.

**Maintenance of Wakefulness Test in practice**

The MWT has no diagnostic value for a specific sleep disorder. Its main application is the quantification of sleepiness. Compared to the MSLT, the MWT is more sensitive to detect improvement, e.g. in pharmacological trials for EDS. The MWT may also be indicated in assessment of individuals in whom the inability to remain awake constitutes a safety issue. There is little hard evidence, however, linking mean sleep latency on the MWT with the risk of accident in the real-world situation. For this reason, the sleep clinician should not rely solely on mean sleep latency as a single indicator of impairment or risk for accidents, but also rely on clinical judgment [4].

**Key points**

- The MSLT is the most widely used objective test for the assessment of daytime sleepiness. It is mainly used for diagnostic purposes.
- The MWT is used for the quantification of daytime sleepiness.
- Although the MSLT is the best available test for the assessment of pathological sleepiness, the sensitivity and specificity are too low to use it as diagnostic on its own. Results always need to be interpreted in the clinical context.

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## CHAPTER 4

# Nosological classification and diagnostic strategy

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## Introduction

In the previous three chapters, the basic "tools" to achieve a specific diagnosis of sleep disorder have been described. However, putting together all the information provided by a comprehensive battery comprising a detailed history, nocturnal sleep studies and daytime tests is often not straightforward. In particular, sleep disorders are not always seen in a "pure" state. For example, given the high prevalence of sleep-disordered breathing, it is not rare to encounter a patient with psychophysiological (conditioned) insomnia who also suffers from sleep apnea. Complex symptomology and pathophysiology are even commoner for sleep disorders associated with neurological diseases.

This chapter introduces the current classification of sleep disorders: the second edition of the *International Classification of Sleep Disorders* (ICSD-2). Published in 2005, this forms a useful and comprehensive framework to direct diagnostic efforts.

An increasing number of sleep questionnaires are becoming available. These can sometimes be of help at the start of the diagnostic process and some of the more widely used questionnaires are described.

A final diagnosis and management plan will often depend on clinical data together with information provided by sleep studies. The importance of a systematic approach will be illustrated by case examples.

## Classifications

The *International Classification of Sleep Disorders* is a concise reference book with information on the presently known disorders of sleep. The diagnostic

framework results from consensus meetings of a large group of professionals selected by the American Academy of Sleep Medicine [1]. ICSD-2 classifies the various sleep disorders based on the following categories: insomnias, sleep-related breathing disorders, central hypersomnias, circadian rhythm disorders, parasomnias, and sleep-related movement disorders. In addition, a section deals with “isolated symptoms” such as primary snoring or variants of sleep that might be considered within the normal range such as sleep talking. When a neurological disorder is accompanied by sleep symptoms, the sleep disorder determines the diagnostic category in the ICSD-2 with the addition of “due to medical disorder.” However, ICSD-2 does discuss several medical syndromes separately, such as fatal familial insomnia, fibromyalgia, and sleep-related epilepsy.

The coding framework of the ICSD-2 is essentially different from more widely used general medical classification systems, such as the *International Classification of Diseases* (ICD, currently in its tenth edition). In ICD-10, the neurological disease should be coded as the primary diagnosis. Furthermore, not all sleep disorders are represented in the ICD-10. To facilitate the coding of sleep disorders when using ICD-10, a framework for converting ICSD-2 diagnosis to ICD-10 codes is presented in Appendix A of the book. At present, many neurological disorders with prominent sleep-wake symptoms are not specifically mentioned in the ICSD-2. Table 4.1 lists most of these disorders, many of which are discussed in detail in other chapters of this book.

## Sleep questionnaires

A detailed sleep history is clearly crucial in achieving an accurate diagnosis but time constraints and inexperience with managing sleep-disordered patients may pose problems for general neurologists. In selected patients, therefore, standard questionnaires may be usefully applied to assess the presence and/or severity of sleep-related symptoms. Many such questionnaires are available (Table 4.2). Some of these focus on a single symptom such as daytime sleepiness while others attempt to aid diagnosis of specific disorders such as obstructive sleep apnea. Of course, questionnaires can never replace a thorough history, and should always be used with caution (see case 1 at the end of this chapter).

Some of the questionnaires used both in clinical practice and in scientific studies are discussed below.

The *Epworth Sleepiness Scale* (ESS) is by far the most frequently used self-administered questionnaire to evaluate daytime sleepiness [2]. Patients are asked to rate the likelihood of dozing off in eight different situations on a 4-point scale. The total score, therefore, potentially ranges from 0 to 24.

**Table 4.1** Sleep disorders that are classified in the ICD-10 as “neurological,” together with neurological diseases that are often accompanied by sleep disturbances, but are not mentioned in the ICSD-2. Most diseases are discussed in detail elsewhere in this book

Neurological disease	ICD-10 code
Narcolepsy	G47.4
Idiopathic hypersomnia	G47.1
Kleine-Levin syndrome	G47.8
Fatal familial insomnia	A81.8
RLS	G25.8
PLMD	G25.8
RBD	G47.8
Fibromyalgia	M79.6-/70
Sleep-related epilepsies	G40.2–40.8 + G47.0/1
Status epilepticus in sleep (CSWS)	G41.8
Sleep-related headaches	
Migraine	G43.x
Cluster headache	G44.0
Chronic paroxysmal hemicrania	G44.0
Hypnic headache	
Neuromuscular diseases	
Dystrophia myotonica	G71.1
Curschmann-Steinert	
Myopathies	G71.2–73.7
Myasthenia gravis	G70.x
Amyotrophic lateral sclerosis	G12.2
Guillain-Barré syndrome	G61.0
Polyneuropathies	G60-63
Multiple sclerosis	G35.x
Cerebellar ataxias	
Spinocerebellar ataxia, SCA 1-6	G11.x
Hereditary ataxia	G11.x
Extrapyramidal diseases	
Parkinson’s disease	G20
Chorea Huntington	G10
Dystonias	G24.x
Multisystem atrophy (MSA)	G23.2/8, G90.3
Corticobasal degeneration (CBD)	G23.8
Progressive supranuclear palsy (PSP)	G23.1
Dementia of Lewy-body type (DLB)	G31.88
Alzheimer dementia (AD)	G30.x
Cerebrovascular diseases	I60-68
Head trauma	S06.x
CNS tumors	C70–72, D32–33, D42–43

**Table 4.2** Questionnaires often used in sleep medicine

Name	Abbreviation	Diagnostic targets	Reference
Epworth Sleepiness Scale	ESS	Evaluation of daytime sleepiness	Johns 1992 [2]
Stanford Sleepiness Scale	SSS	Evaluation of daytime sleepiness on a continuous, hourly scale	Hoddes et al. 1973 [3]
Pittsburg Sleep Quality Index	PSQI	Severity of sleep disorders	Buysse et al. 1989 [4]
Berlin Questionnaire		Prediction of sleep apnea	Netzer et al. 1999 [5]
Ulanlinna Narcolepsy Scale	UNS	Distinguishes narcolepsy from sleep apnea, multiple sclerosis and epilepsy	Hublin et al. 1994 [6]
REM sleep behavior disorder screening questionnaire	RBDSQ	REM Sleep Behavior Disorder	Stiasny-Kolster et al. 2007 [7]
Munich Parasomnia Screening	MUPS	Parasomnias	Fulda et al. 2008 [8]
Sleep EVAL		Assessment of Sleep Disorders according to ICSD and DSM-IV	Ohayon 1994 [9]
Structured interview for sleep disorders according to DSM-III-R	SKID	Provides interview techniques to obtain correct diagnosis according to DSM-III-R	Schramm et al. 1993 [10]
SF-36	SF-36	Health-related quality of life	Ware & Gandek 1998 [11]
EuroQuol	EQ-5D	Health related quality of life	EuroQuol Group 1990 [12]

Generally a score above 10 is regarded to indicate significant and excessive daytime sleepiness, although several authors feel that a cut-off of 12 provides a better trade-off between sensitivity and specificity. Scores of zero or 24 should generally arouse suspicion.

The ESS measures daytime sleepiness over the past month. In contrast, another commonly used scale, the *Stanford Sleepiness Scale* (SSS), is designed to probe the contemporaneous feeling of sleepiness [3].

The *Pittsburg Sleep Quality Index* is a detailed questionnaire evaluating nocturnal sleep quality over the past month [4]. It comprises 18 self-rating questions and 5 questions to be filled in by the partner, if present. The 18 questions are divided into seven components which yield a component score between 0 and 3, which are then added for a global score. The components probe subjective sleep quality, sleep latency, sleep duration, sleep efficiency, several symptoms of specific sleep disorders such as sleep apnea, consumption of hypnotics, and daytime sleepiness. An empirical cut-off score of 5 allows discrimination of “bad” from “good” sleepers. However, the

PSQI is not suited for differential diagnosis in clinical practice. Evaluation at a group level, however, allows the component scores to have value assessing different aspects of nocturnal sleep quality.

The *Berlin Questionnaire* is a validated explorative tool of 13 questions designed to identify patients with obstructive sleep apnea. The questions are targeted toward key symptoms such as snoring, witnessed apneas, daytime sleepiness, and obesity [5]. The questionnaire has been shown to identify patients with a respiratory disturbance index of  $>5$ /hour with good reliability.

The *Ulanlinna Narcolepsy Scale* was designed to probe the two core symptoms of narcolepsy – EDS and cataplexy [6]. It has good discriminative properties, at least in a validation study against patients with sleep apnea, multiple sclerosis, and epilepsy.

Other questionnaires directed towards specific sleep disorders are the *International Restless Legs Severity Scale* [13], the *Munich parasomnia screening* [8], and the *REM sleep behavior disorder screening questionnaire* [7].

A different approach is taken by the *Sleep EVAL* system, a knowledge-based computerized expert system that allows the diagnosis of the main sleep disorders from the ICSD [9]. The system uses the interviewee's response as direct input, rather than the interviewer's judgement. Depending on the answers given, a decision tree is systematically followed. The time needed to complete a Sleep EVAL interview therefore varies widely with a range from 10 minutes to more than an hour.

Sleep disorders often co-occur with psychiatric disease. The Structured Clinical Interview for DSM Disorders (SCID) is a validated diagnostic based on the DSM-III-R psychiatric classification system [10]. Finally, health-related quality of life can be assessed by specific questionnaires such as the *EQ-5D* or *SF-36* [11].

## Reaching a diagnosis

Perhaps more than most medical specialties, reaching a reliable diagnosis in sleep medicine can be less straightforward than anticipated. Symptoms are often more complex than at first appears and uncertainties frequently lead to "probable" diagnoses. A common first hurdle is for the subject actually to acknowledge there is a sleep problem, as symptoms are frequently misinterpreted. For example, EDS is regularly dismissed as tiredness which could, in theory, be solved by going to bed a little earlier. It is only when both patient and physician acknowledge that there is some kind of sleep-wake pathological process that the diagnostic process can start. In many cases, the medical history, with or without the addition of questionnaires, is sufficient to reach an initial differential diagnosis. Diagnostic doubt in

more difficult cases usually requires one or more objective sleep tests such as polysomnography. The diagnosis of certain sleep disorders, especially if there is combined or complex pathology, often requires specialized attention and investigation in an accredited sleep center.

The data gathered by questionnaires, the clinical interview, and additional technical procedures should be integrated into a logical framework that provides a working hypothesis, differential diagnosis, and eventually a final, confirmed diagnosis. In this process, additional medical comorbidity should always be taken into account. This holds true not only for a primary neurological disorder, but also for many other diseases such as psychiatric, endocrine, or pulmonary disturbances.

### **Translating the complaints**

From the medical history, a list of reported complaints is compiled, such as “falling asleep during activity,” “inability to concentrate upon awakening,” or “itching of the legs.” These complaints should then be translated into formal symptoms: “excessive daytime sleepiness,” “sleep inertia or drunkenness,” “restless legs.” The next step is to formulate a working hypothesis that points to a disease according to the ICSD-2 criteria: possible obstructive sleep apnea syndrome, restless legs syndrome. Chapter 1 provides detailed information on important points to include in a directed history.

Sometimes the array of symptoms seems so classical that a specific diagnosis jumps out very early in the interview. However, it is generally recommended to follow a structured interview of all general aspects of sleep and address the symptoms prominent in potential other sleep disorders. For example, information on normal bed times and sleep hygiene should always be sought. Routine screening for restless legs, nocturnal movements, and sleep apnea symptoms is also mandatory. Finally, a drug history may reveal agents potentially disturbing sleep or masking certain complaints. If the diagnostic trajectory is focussed towards one specific disorder too soon, one may easily miss the correct diagnosis (see case 2 at the end of this chapter). In addition, the information from the general sleep interview may be of help with treatment. For example, even though narcolepsy patients usually merit drug treatment, improving ingrained bad sleep habits such as an irregular sleep-wake schedule may be very beneficial to individual subjects.

### **The need for additional tests**

Sleep tests are not only potentially useful when a clinical diagnosis is uncertain. Besides clarifying a differential diagnosis, sleep-related investigations may be required to assess the presence and degree of comorbid sleep disorders. At the very least, tests usually provide insight into the severity

of the disorder in a relatively objective way. Furthermore, the diagnosis of certain primary sleep disorders such as narcolepsy may have important psychosocial, legal, and treatment consequences. This makes it important to make every effort to reach a firm, certain, and objective diagnosis.

The performance and interpretation of sleep investigations are covered in chapters 2 and 3 of the book. It should be emphasized, however, that interpretation of polysomnographic recording never stands alone. Failing to include relevant information from the medical history is guaranteed to produce erroneous conclusions (see case 3).

### **“Diagnostic treatment”**

Sometimes it can be helpful to start a treatment in the context of a working diagnosis, not only for the benefit of the patient but also as a diagnostic aid. For example, if bad sleep hygiene is picked up in a patient with excessive somnolence, this should be initially addressed and appropriate advice given. The same holds true when withdrawing or changing medications or substances that are likely to disturb sleep. When these measures do not lead to resolution of daytime somnolence, further testing can then be considered. Another situation is the sleepy patient with reported snoring but a low apnea index recorded on nocturnal polysomnograph. If a therapeutic trial of continuous positive airway pressure (CPAP) treatment is undertaken for a few weeks and leads to clear improvement of nocturnal sleep with disappearance of daytime sleepiness, significant sleep-related breathing disorder can be assumed. Although this empirical approach can be helpful, it is essential to decide clearly beforehand how long a treatment trial will be attempted and what are the parameters for treatment success or failure. This helps to avoid unnecessary treatments in patients when beneficial effects are, at best, doubtful.

### **The sleep specialist**

The skills to reliably diagnose current sleep disorders is obviously within the scope of most general neurologists. However, when diagnostic doubt remains, it is recommended to consult a sleep specialist at an early stage so that specific sleep tests can be considered. A sleep physician may also be required when the presence of another medical disorder interferes with the diagnostic process. This also holds true for primary sleep disorders in which a definite diagnosis has significant consequences for daily activities such as narcolepsy, or if potentially complex treatments need consideration. Following diagnosis, a sleep specialist is best placed to decide on the most appropriate therapeutic strategy whether this is positive airway pressure therapy for sleep-disordered breathing, multidrug regimens for narcolepsy, cognitive behavioral therapy for insomnia, or even a combination of all three.

It is increasingly common for a sleep specialist to uncover a previously unrecognized neurological or other medical disorder. For example, REM sleep behavior disorder is now considered to be a reliable premotor manifestation of a parkinsonian syndrome. Probably in every patient with established RBD, the sleep specialist should consider the presence of a neurodegenerative disorder, potentially subclinical, and refer appropriately. Another example is EDS as a sign of nocturnal hypercapnia in patients with undiagnosed neuromuscular disease. Close collaboration between the sleep specialist and the neurologist may not only yield a complete and proper diagnosis but have important implications for management. Treating the symptoms of sleep-disordered patients not only improves quality of life but may also help to circumvent significant medical consequences. For example, it is likely that in the case of sleep-related breathing disorders, morbidity and mortality due to potential cardiovascular sequelae such as stroke and ischemic heart disease can be positively influenced by the use of nasal ventilation therapy [14,15].

### Key points

- The *International Classification of Sleep Disorders* provides a comprehensive framework for the diagnosis of all recognizable sleep disorders although does not always highlight a sleep disorder when embedded in a neurological syndrome.
- Sleep questionnaires are never a substitute for a detailed history but may provide a useful and efficient screening tool to pick up sleep-related symptoms in a variety of populations.
- Sleep investigations may provide additional information to improve diagnostic confidence and reveal unsuspected or comorbid sleep pathologies.
- It is sometimes appropriate to consider a trial of treatment as part of the diagnostic process, provided clear guidelines for gauging any response are in place.
- Many patients benefit from the involvement of both sleep physicians and neurologists in the management of sleep-related symptoms within neurological disease.

### Case 1 – Care with questionnaires

A 56-year-old man with Parkinson's disease was referred for problems with sleep maintenance. He did not indicate specific nocturnal events on a general sleep questionnaire but scored very high on the REM Sleep Behavior Screening Questionnaire. A detailed history, however, revealed that he was most likely suffering from sleep walking. The information in the questionnaire turned out to reflect "second hand details" from his wife because he, himself, was totally amnesic for his nocturnal disturbances. The wife's report on his nocturnal actions had been very dramatic with descriptions of aggressive behaviors. The patient himself had no recall of his recent nocturnal actions but recalled that he frequently wandered around at night as a child. In particular, his mother had told him that his eyes were always open and he looked very "blunt," typical of sleepwalking. This case shows that questionnaires can give wrong



directions, especially in cases where a specific diagnosis such as RBD is quite likely a priori. Historical details that are the clue to the right diagnosis are usually only picked up in a clinical interview by an experienced physician. In this case, the lack of dream recall on apparent arousal, the detailed nature of the motor disturbance, the fact that he frequently left the bed together with a prior history of likely sleep walking all made RBD less likely than a non-REM parasomnia as a working diagnosis.

### Case 2 – A sleep disorder may not come alone

A 40-year-old male presented in the sleep clinic because of persisting severe daytime sleepiness despite CPAP therapy for earlier diagnosed obstructive sleep apnea. Previously, at the age of 36, the patient had consulted a physician in a pulmonary sleep laboratory to assess his longstanding sleepiness. The referral had been prompted by a number of failed exams after a management course at work. In a state of severe drowsiness, he had written nonsense prose in a presumed state of automatism and, as a consequence, had failed.

A polygraphic study revealed severe obstructive sleep apnea (AHI = 56/h). Nasal CPAP treatment at a pressure of 11 cm H<sub>2</sub>O was initiated and the patient showed good compliance. He felt that his EDS improved during the first 4 months after the start of the treatment. Indeed, a repeat study at the age of 38 did not show any apneas under CPAP treatment. However, he still complained about severe EDS. Furthermore, he reported “breaking away of legs,” when scolding his children or telling jokes. He was then referred to a general sleep clinic.

A thorough medical history revealed that, even at the age of 19, when joking around with friends, he would buckle at the knees. In addition, he often felt asleep at school and classmates regularly had to waken him during classes. In the clinic, several other complaints were picked up:

- suddenly falling asleep during the daytime;
- recognizing his sleepiness only by looking at mistakes made whilst writing, often illegibly;
- buckling of the legs one or two times a day, sometimes with falls;
- frequent short nocturnal awakenings, even with CPAP treatment;
- nocturnal talking, sometimes accompanied by aggressive movements of the arms and legs, disturbing the sleep of his wife.

A Multiple Sleep Latency Test was performed, showing a mean sleep latency of 4.4 minutes and three sleep onset REM periods. This confirmed a diagnosis of narcolepsy/cataplexy, and treatment with stimulants and antidepressants for cataplexy was initiated.

This patient shows that complaints not recognized as part of a sleep disorder may be present for many years before a sleep specialist is consulted. Even then, only the most prominent complaints are spontaneously reported. To establish a final diagnosis, the whole array of symptoms of a suspected sleep disorder has to be scrutinized. Furthermore, in every patient a general sleep history has to be taken. Given the high prevalence of certain sleep disorders such as sleep apnea, it is not uncommon to encounter patients with more than just one disease. In this case, the recognition of cataplexy would have prevented the considerable delay of over 4 years before appropriate treatment was started.

Case 3 – History, history, history

A 42-year-old man was referred from a peripheral hospital to the sleep clinic. He had been a normal sleeper until 10 months previously. At that time, he had a traffic accident whilst biking and was hit by a car from behind. He was flung onto the hood of the car, receiving a blow on the back of the head, rendering him unconscious for several minutes. He was examined during a short hospital admission for a mild traumatic brain injury, requiring only relative rest. After a few weeks, he began to suffer from insomnia with initial problems of sleep maintenance. Later, the initiation of sleep also became a major issue as well. This condition progressively worsened to the extent that he was unable to go to work. Whilst his sleep was reportedly very bad, he was not particularly sleepy during the daytime. A polysomnography scheduled in the general hospital showed a long sleep latency but a relatively normal sleep architecture thereafter. There were no frank apneas but frequent hypopneas (105) with an index of 17.8/h (see figure 4.1).

The polysomnography was reviewed by both a neurologist and a pulmonologist. The former established a diagnosis of delayed sleep phase syndrome (DSPS), based on the long sleep latency and the subsequent stretch of relatively stable sleep. He prescribed melatonin 3 mg before bedtime. The pulmonologist concluded that he also suffered from obstructive sleep apnea syndrome and recommended treatment with nasal CPAP.

Melatonin resulted in better sleep initiation although this effect was lost after 2 weeks. The patient could not tolerate nasal CPAP as it worsened his insomnia. He was then referred to the sleep clinic because of treatment failure. All necessary diagnostic steps for diagnosis were repeated, starting with a thorough history of the actual symptoms.

The history was consistent with acute-onset insomnia pursuing a subsequent progressive chronic course. The accident served as the primary triggering event. The delay of several weeks between the event and the onset of sleep symptoms also suggested a psychological rather than a physical (“organic”) consequence of the accident. When the patient could not fall asleep, or woke up after sleep onset, he would start to worry. Ruminations about his health and fitness to continue his job were the main recurrent themes. When unable to sleep, he became very tense and restless. He tossed and turned, and frequently checked his alarm clock. Overall, the history was very consistent with psychophysiological insomnia.

The insomnia culminated in absence from work for 3 months. A course of zopiclone 7.5 mg at bedtime gave temporary relief. It was not until he received cognitive

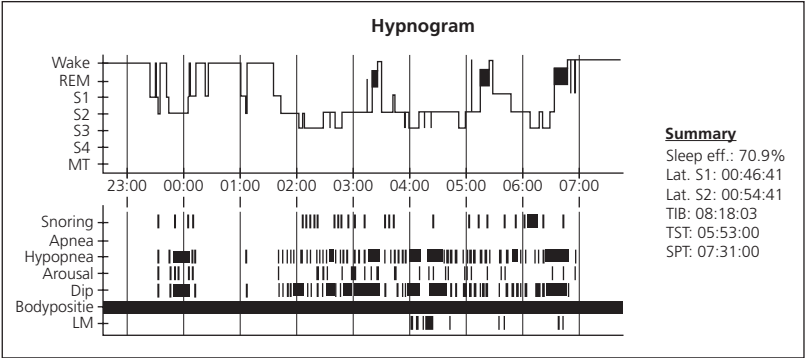


Figure 4.1 Polysomnography summary.

behavioral therapy that his condition improved substantially. He gradually slept better and was able to fall asleep faster after nocturnal awakenings. He had learned not to watch the clock and had reduced sleeping pills to one or two times a week. He had resumed his work on a part-time basis.

It appeared that his initial assessments had not properly taken the history into consideration when coming to a final conclusion. The delay in sleep onset on the polysomnograph recording actually reflected sleep-onset insomnia, rather than being a sign of a circadian rhythm disorder. The elevated number of hypopneas was obtained from automated scoring which may often overestimate the hypopnea index. Most importantly, the patient's actual history was not suggestive for sleep-related breathing problems.

This case illustrates that all pieces of diagnostic information must be taken into account. Furthermore, these steps must be consecutive and start with a detailed history. In this case, the working hypothesis should have been "psychophysiological insomnia" right from the beginning. This would have changed the conclusions taken from the polysomnographic recording and may even have obviated the need for a recording in the first place.

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## **PART II**

# Management of Sleep Disorders

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## CHAPTER 5

# Pharmacological treatment of nocturnal sleep disturbances

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### Introduction

In neurological practice the full range of sleep disorders is commonly encountered. This chapter will focus on the pharmacological treatment of nocturnal sleep problems of which chronic insomnia, as defined by impaired sleep onset and/or maintenance, is commonest. The treatment, if required, of parasomnias will also be covered. Although parasomnias are generally divided into those arising from either non-REM or REM sleep, treatment options do not differ greatly.

### Sleep-onset and sleep-maintenance insomnia

Overall, insomnia is the most common sleep disorder in the general population with somewhere around 10–15% of the adult population reporting chronic symptoms [1,2]. Symptomatically, insomnia is rather loosely defined as a persistent problem, lasting at least one month, of sleep initiation, consolidation, duration, or quality despite the opportunity to sleep adequately [3]. Overall, it is estimated that primary insomnia accounts for about 15% of all insomnia cases. The majority (85%) have secondary factors which promote or even cause the sleep disturbance. These include neurological, psychiatric, and other medical conditions, substance abuse, as well as lifestyle factors.

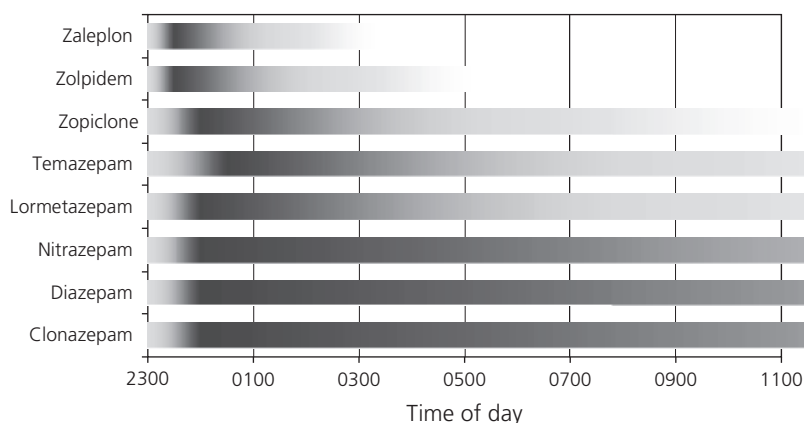
Whether insomnia is predominantly “primary” or “secondary,” assuming provoking factors have been addressed, available drug treatments are essentially very similar. However, it is important to recognize the precise nature of a patient’s insomnia with respect to sleep onset or sleep maintenance as this will influence the choice of drug. Problems staying asleep are particularly common in the elderly and will more often be seen in neurological practice.

It is important to recognize insomnia not only because of the huge negative impact it can have on quality of life but also because of its implications for public health. For instance, subjects with insomnia have up to a four-fold risk of subsequently developing depression [4]. Unfortunately, there are several issues and problems faced by doctors treating insomnia. First, drug treatments are often subject to guidelines recommending strict restrictions on the length of prescribing, conflicting with the long-term nature of most patients' symptoms. Second, although behavioral therapies are often recognized as the most effective treatment, certainly for primary insomnia, such nonpharmacological forms of treatment generally have extremely limited availability in public health systems.

### Choice of hypnotic medication

Many patients will have tried over-the-counter (OTC) sleep remedies before consulting the medical profession. These usually contain antihistamines with a relatively long duration of action and the subsequent potential for daytime sedation. Regarding herbal sleep aids, such as lavender, there are very few randomized clinical trials [5] and, so far, convincing evidence for efficacy is inconsistent.

In the clinical setting, an appropriate choice of hypnotic would be a drug whose absorption and elimination characteristics suit or match the patient's problem: that is, a fast-acting and short-lasting drug for someone whose only problem is falling asleep, or a slower-acting and longer-lasting agent for someone who has problems with sleep interruptions later in the night (see figure 5.1 and table 5.1).



**Figure 5.1** Graphic depiction of plasma levels of some typical hypnotic drugs, taken at 23.00 h. The depth of shading corresponds to plasma levels.



**Table 5.1** Benzodiazepines and benzodiazepine receptor-agonist ("Z") hypnotic drugs

	Usual dose	Rapid onset	Elimination half-life (h)	Daytime (hangover) effects	Safety
Zopiclone	7.5 mg	+	3.5–6	?Yes	✓
Zolpidem	10 mg	++	1.5–3	No	✓
Zaleplon*	10 mg	++	1–2	No	✓
Temazepam	20 mg		5–12	?Yes	✓
Loprazolam	1 mg		5–13	?Yes	✓
Lormetazepam	1 mg	+	8–10	?Yes	✓
Nitrazepam	5–10 mg	+	20–48	Yes	✓
Lorazepam	0.5–1 mg	+	10–20	Yes	✓
Diazepam	5–10 mg	+	20–60	Yes	✓
Oxazepam	15–30 mg		5–20	Yes	✓
Alprazolam	0.5 mg	+	9–20	Yes	✓
Clonazepam	0.5–1 mg	+	18–50	Yes	✓
Chloral hydrate/betaine	0.7–1 g	+	8–12	?Yes	×
Chlormethiazole	192 mg	+	4–8	?Yes	×
Barbiturates	varies	+	varies	Yes	×

\*Can be taken during the night, until 5 hours before needing to drive, etc.

Specifically in a neurological setting, where the sleep symptoms may be more complex, an empirical approach is often required. Furthermore, if an extended duration of treatment is anticipated, it is often more acceptable to recommend drugs not considered typical "hypnotics." For example, if sleep maintenance is a major symptom and reduced levels of presumably restorative deep slow-wave sleep are thought likely, then an agent that increases the relative amount of deep slow-wave sleep would be a logical suggestion.

## Benzodiazepines and "Z" drugs

### Mode of action

Most hypnotic drugs used to aid sleep onset act by enhancing the function of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) in the brain. The associated increased inhibitory transmission can lead to a combination of sedative, anticonvulsant, and anti-anxiety effects. Benzodiazepines and the nonbenzodiazepine "Z" drugs (zopiclone, zolpidem, and zaleplon) are generally effective hypnotics [6] that have an agonist effect at a modulatory site on the GABA-A receptor, effectively enhancing the inhibitory effects of GABA. Taken in overdose they have favorable safety characteristics since they enhance the effect of an endogenous transmitter. As a result, their sedative and respiratory depressant effects are limited by the availability of this transmitter such that they are

not lethal when taken alone. However with the addition of alcohol or other drugs which have the ability to directly affect the GABA-A receptor, this relative safety in overdose is compromised.

The shortest-acting benzodiazepines are temazepam, lorazepam, and lormetazepam with half-lives of up to 12 hours. Zopiclone has a half-life of 6–8 hours, and is usually an effective drug both for initiating and maintaining sleep. Zolpidem and zaleplon have a fast onset (30–60 min) and short duration of action, with half-lives of 3 and 2 hours, respectively. A longer-acting extended-release formulation of zolpidem is available in some countries. Studies in volunteers have shown that zaleplon has no effect on psychomotor performance including driving skills when taken at least 5 hours before testing. This means that it can be taken during the night, either when patients have tried getting off to sleep for a long time, or if they wake during the night and cannot return to sleep, without hangover effect. It is the only prescribable hypnotic that can be used in this way. Patients find it reassuring because it means that they do not have to take a drug every night but feel they have medication potentially available, increasing confidence about sleeping and reducing associated worry.

Objective measures of sleep show that these hypnotics decrease the time to sleep onset and reduce waking during the night. The subjective effects of improved sleep are usually greater than the objective changes, probably because of the anti-anxiety properties of these drugs. Other changes in sleep architecture are dependent on duration of action, with the very short-acting compounds having the least effect. Usually very light (stage 1) sleep is decreased and stage 2 sleep is increased. Higher doses of longer-acting drugs partially suppress slow-wave sleep.

Other drugs that act on the GABA-A benzodiazepine receptor and enhance GABA function are chloral hydrate, clomethiazole, and barbiturates. However, at high doses they have the additional capacity directly to open the membrane chloride channel. This may lead to potentially lethal respiratory depression and explains their low therapeutic ratio. These drugs also have a propensity for misuse and are therefore considered very much as second-line treatments.

### **Side effects and other issues**

GABA-ergic drugs have side effects which include muscle relaxation, memory impairment, and ataxia. These may not be a problem when the patient is asleep but if it is necessary to get up during the night, especially if elderly or physically disabled, or if the action of the drug is prolonged past the time of arousal, then these effects can become very important. Those with longer duration of action are likely to affect memory, concentration, and performance in skills such as driving the next day. However, the daytime anxiolytic and muscle-relaxing effects which also persist can be helpful in some people.

Care should be taken in prescribing GABA-ergic drugs to patients with comorbid sleep-related breathing disorders, such as obstructive sleep apnea syndrome, which may be exacerbated by benzodiazepines in particular. Another very important point is that alcohol potentiates the effects of these drugs, and patients should be made aware that if they have had a drink in the evening, their sleeping pill will have greater and longer-lasting effects, possibly impacting on driving the next day.

Topics which worry patients and particularly their doctors when considering the use of hypnotics are those of tolerance, dependence, and withdrawal. Hypnotic drugs are licensed for short-term use and we have found that many insomnia patients can be frightened by their experience of stopping sleeping pills. There is almost always a short-term rebound of poor sleep, interpreted as a pressing need to start taking them again. When it is explained that this rebound is likely even in good sleepers in research studies, they often respond positively.

For patients who wish to stop their hypnotics there are various strategies. One is to encourage intermittent use of short-acting hypnotics, so that the patient knows they will get a good night's sleep two or three times a week with medication, helping them to cope with the bad nights. Another is to encourage dose tapering over a short period with education of the patient about rebound insomnia. Psychological interventions such as those involving cognitive behavior therapy (CBT) may also provide the patient with strategies which will make stopping their tablets easier.

There will be some patients in whom it is difficult to ameliorate the sleep-disruptive factors which perpetuate their insomnia, or who continue to complain that their insomnia responds only to drugs. In such cases, the patient and clinician together need to weigh up the risks and benefits of remaining on medication, bearing in mind the possible risk of the patient using alcohol or unprescribed drugs as an alternative. There is now some data on continuing long-term efficacy of the active (S) enantiomer of zopiclone (eszopiclone) for 6 months [7] and 12 months [8] and also for extended-release zolpidem for 6 months [9].

### **Antidepressants**

Antidepressant classes of drug are commonly used primarily as hypnotic agents even in patients without significant mood disorder. Antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) which have good efficacy in anxiety disorders are often helpful in reducing anxious ruminations about poor-quality sleep. If a typical hypnotic drug is used in combination and is to be withdrawn, the patient should be stabilized on a standard antidepressant dose before withdrawal of the hypnotic is started.

In depression, mirtazapine is useful in patients with marked insomnia as a major symptom because of its sleep-promoting properties. It has a receptor antagonist profile which includes blocking histamine H1 and serotonin 5HT2 receptors [10].

Trazodone also blocks 5HT2 receptors and is also often used in depressed patients with prominent insomnia. There has not been a controlled study of its use in insomniac patients who are not clinically depressed although it is widely used for this purpose in the USA. It may also increase slow-wave sleep in both healthy volunteers and depressed patients (for review see [11]), increases total sleep time and efficiency, reduces awakenings, increases slow-wave activity and decreases sleep spindles [12]. Furthermore, it appears to improve sleep in a model of insomnia in healthy volunteers [13].

There is a small amount of data on the use of low doses of the antipsychotic quetiapine to improve sleep. It is primarily an atypical neuroleptic but also acts as an H1/5HT2 blocker with  $\alpha$ 1-adrenoceptor antagonism. However, drugs of this class may have long-lasting actions on sedation and have effects beyond the sleep-inducing brain systems, producing potential unfavorable side-effect profiles.

An alternative but non-recommended strategy used by very many general practitioners, at least in the UK, is to prescribe low doses of sedating tricyclic antidepressants (TCAs), usually amitriptyline, for improving sleep. However, there is no objective evidence that very low doses of tricyclic antidepressants improve sleep long-term in primary insomnia. Doxepin 25 mg was shown to have a modest efficacy in a 4-week study [14], attributed to its antihistamine effects. One reason for not using tricyclics is that these drugs are the commonest cause of suicide by self-poisoning with drug [15]. The side-effect profile of weight gain and dry mouth is often also prohibitive. Furthermore, if restless legs or periodic leg movements are partly fueling insomnia, these drugs are likely to worsen the situation.

## Melatonin

Melatonin is the natural hormone produced by the pineal gland during darkness. Administration of exogenous melatonin has been investigated for insomnia because it assists sleep in circadian rhythm disorders when phase is altered, such as during jet lag. However, its efficacy in primary insomnia is questionable [16], perhaps because it is very quickly metabolized. A modified release formulation of synthetic melatonin that prolongs the effective half-life has shown significant effects to improve subjective quality of sleep and daytime function in insomniacs over 55 years old [17]. In this age group there is some evidence of reduced endogenous melatonin

rhythm. There were no significant daytime sedation or withdrawal effects. This new synthetic melatonin agonist, ramelteon [18], produces shortening of sleep latency in sleep-onset insomnia, and shows no cognitive, motor, or respiratory-related side effects.

Melatonin is well tolerated although some patients report significant body cooling, perceived an hour or two after ingestion. This presumably reflects a physiological action of the drug on circadian temperature control.

## **Other drugs to improve sleep maintenance**

### **Sodium oxybate**

There has been a renaissance of interest in sodium oxybate as a treatment for cataplexy and the other core symptoms of narcolepsy. Given before bed, it has marked and interesting effects on sleep quality subjectively and objectively. It is the sodium salt of gamma-hydroxybutyric acid (GHB) which probably acts mainly through GABA-B receptors in the brain. However, a neurotransmitter system with specific GHB receptors has also been described [19]. The drug may also be metabolized to GABA, thereby affecting GABA-A receptors too. Outside medical practice, it is a drug that is abused for its euphoric, intoxicating, and growth-hormone promoting effects. Its half-life in plasma is very short but its central effects are somewhat longer lasting.

Its effects on sleep are to shorten sleep latency, reduce waking and markedly increase slow-wave sleep. In narcolepsy, it appears to reduce the characteristically fragmented nocturnal sleep pattern and may “normalise” sleep architecture, consolidating both non-REM and REM sleep elements [20]. Certainly, in healthy volunteers it has the effect of decreasing stage shifts, particularly from REM sleep [21].

In narcolepsy it is given in doses of up 9 g per day in two doses, one at bedtime and one around 2–4 hours later. It is a controlled drug in most countries and dispensing is regulated largely due to its perceived abuse liability, particularly as a “date rape” drug.

Because of its properties, sodium oxybate is also under investigation for a variety of sleep-related conditions, including fibromyalgia, Parkinson’s disease [22], and REM sleep behavior disorder (RBD). In a small series of patients with RBD and narcolepsy, the RBD episodes disappeared during routine treatment with sodium oxybate [23].

### **Gabapentin and pregabalin**

Although not licensed primarily for sleep-related problems, gabapentin and, in particular, pregabalin, are increasingly used by sleep physicians to treat sleep-maintenance insomnia, especially if anxiety or pain symptoms

predominate. These drugs are more commonly used as neuropathic pain agents but have the rare property of enhancing slow-wave non-REM sleep [24]. This may improve subjective feelings of morning refreshment for patients in whom sleep is generally fragmented and/or dominated by light stage 2 non-REM sleep.

## **Parasomnias**

Recognition and diagnosis of these nocturnal disturbances are described fully in chapter 16. Simply having a formal diagnosis of parasomnia is often reassuring to patients, as they often fear epilepsy or that their nocturnal disturbances somehow reflect insufficient self-control. They also report both guilt about the effect the night-time disturbance has on family or house-mates and fear regarding the potential harm they may inflict on themselves or others. Indeed, there is an increasing medico-legal literature as testament to this rare but distinct latter possibility.

The majority of parasomnias do not justify drug treatment, especially if the patient is young and the disturbances are either mild or infrequent. However, particularly if violence is feared or has occurred, pharmacological treatment should be discussed and offered, even if only on an intermittent basis.

Unfortunately, drug treatment of these disorders has an extremely small evidence base as severe examples are relatively rare or, at least, unpredictable, making controlled studies very difficult. However, there are enough case series and small studies to give a basis for therapy.

### **Non-REM parasomnias – night terrors and sleepwalking**

A first step should assess and treat potential trigger factors for any parasomnia. Most non-REM parasomnias are considered as “disorders of arousal” in which a behavioral event occurs when a subject arouses abnormally and partially from the first cycle of deep slow-wave sleep. Episodes therefore tend to arise either if sleep is abnormally deep, especially following sleep deprivation, or if there are particular arousing factors such as an uncomfortable sleeping environment, severe snoring, or restless legs. Attention to issues of sleep hygiene may prove very helpful, especially in young adult populations.

Sometimes alcohol may increase the risk of night terror or sleep walking, probably because it deepens slow-wave sleep especially at the beginning of the night. A full bladder may also act as an arousing stimulus. Anecdotally, episodes are more common and potentially more dangerous when sleeping in a strange environment. For instance, escape behavior is a common manifestation of non-REM parasomnias and is dependent

on the door being in its familiar place in the bedroom. If it is not, then attempted escape via stairs or a window may cause injury. Many people prepare for this possibility by taking locks with them to secure doors and windows when sleeping away from home. Similarly, patients not keen on regular medication to treat any parasomnia often prefer to take it intermittently, at times of higher risk.

The medication with most evidence for efficacy is clonazepam [25], a benzodiazepine with a long duration of action, which decreases arousals from sleep. Smaller studies have confirmed the efficacy of other benzodiazepines such as diazepam [26], alprazolam [27], and the very short-acting midazolam in children [28]. However none of the patients in the clonazepam studies managed to reduce their dose of benzodiazepines without reappearance of the episodes, and withdrawal from clonazepam can cause a rebound worsening of night terrors.

Paroxetine, an SSRI antidepressant which increases serotonin function through blocking the reuptake site, is also reportedly effective [29]. It can work even after the first dose, implying that the mechanism cannot be the same as that for lifting mood, which usually takes 3–4 weeks. The most likely explanation is a direct pharmacological action to increase serotonin in brainstem regions suppressing ascending arousal pathways. In support of this theory is a controlled study reporting successful suppression of night terrors after daily use of 5-hydroxytryptophan, the serotonin precursor, in children with night terrors [30]. Whether other SSRIs would also work in night terrors has not been established, but our prediction is that they would.

Some patients with severe or nightly terrors will be happy to take paroxetine on a long-term basis. Some wish to try for a few months, and see if the terror “habit” can be broken, which in some of our patients does seem to happen. Medication should be tailed off gradually because there is a risk of rebound after long-term dosing.

### **REM behavior disorder**

Antidepressants, particularly SSRIs, TCAs, mirtazapine, and mixed reuptake inhibitors such as venlafaxine generally make RBD worse or can even cause it. Bupropion may not have this effect but evidence is anecdotal so far.

Clonazepam is effective in the majority of cases in doses of 0.5–2.0 mg [31], although potentially it has daytime sedation effects and may exacerbate breathing problems at night. Some practitioners advocate drug-free days each week to minimize the development of tolerance. Other case reports and small series have shown some benefit from melatonin 5–10 mg [32], the dopamine agonist pramipexole [33], and the alpha-2 adrenoceptor agonist clonidine [34] which probably

acts presynaptically to switch off norepinephrine activity. Patients will usually have to take their medication for the foreseeable future and this should be emphasized to the patient and their treating physician.

### Key points

- Insomnia is disabling to many patients and confers a risk of depression.
- If clear secondary causes have been addressed and drug treatment is considered, it should be tailored to the type of insomnia experienced by the subject.
- Zaleplon is very short-acting and can be used effectively in the middle of the night to reduce sleep onset latency.
- Drugs increasing the slow-wave elements of non-REM sleep such as pregabalin may have a useful role in some insomniacs.
- Tricyclic antidepressants are widely used as hypnotic agents but may worsen overall sleep quality and are dangerous in overdose.
- Most of the common parasomnias do not merit regular drug treatment.
- Clonazepam can be used intermittently for non-REM parasomnias and more persistently for REM sleep behavior disorder.
- Paroxetine may help non-REM parasomnias by a mechanism separate to its antidepressant effects.

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## CHAPTER 6

# Pharmacological treatment of excessive daytime sleepiness

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### Introduction

Alertness of adequately long duration and quality is in every respect essential for good-quality life because of its effect on learning, efficiency, and safety. Excessive daytime sleepiness (EDS) is defined as a reduced ability to maintain continuous wakefulness during the day. EDS may present as lapses into sleep, imperative in some cases. It may also manifest as longer periods of somnolence leading to sleep onset in favorable circumstances. The presence of EDS during activity is a sign of increased severity. It is important to distinguish EDS from fatigue, but this can clinically be very difficult at times. The defining question to ask is: 'do you fall asleep unintentionally during the day?', which is the hallmark characteristic of EDS (see chapters 1 and 19).

Several questionnaires have been developed to assess the presence of EDS, and its severity. The most well known is the Epworth Sleepiness Scale (ESS), which rates the chance of falling asleep in eight everyday situations. ESS scores higher than 10 indicate significant EDS. The ESS can be used to evaluate treatment effects. Objective techniques for the diagnosis of EDS include the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test (see chapter 3), which both have their advantages and disadvantages. Importantly, there often is only a limited correlation between the subjective beneficial effects that certain drugs provide, and changes in the objective tests.

Causes of EDS can be several. A common cause of EDS is self-imposed sleep deprivation, especially in young people. It can also be a side effect of many often-used drugs, for example as a hangover effect of hypnotics. Obviously, nocturnal sleep disturbances can ultimately lead to daytime sleepiness, and should always be assessed and treated. However, in several

conditions, EDS is not a consequence of night-time sleep loss, and should be considered a primary symptom. These disorders include narcolepsy with and without cataplexy, recurrent hypersomnia, idiopathic hypersomnia, and a variety of medical and neurological conditions including Parkinson's disease and other neurodegenerative conditions.

## **General aspects of treatment**

Treatment of EDS starts with the identification of its cause. Sleep deprivation should be corrected. If there is a suspicion that EDS is caused as a medication side effect, it is often necessary to stop the offending drug and evaluate. If night-time sleep disturbances are present, these should be treated accordingly (see chapter 5). However, in many conditions (e.g. Parkinson's disease), there may be a primary form of EDS accentuated by nocturnal sleep disorders and/or medication. Therefore, when improvement of night-time sleep does not lead to resolution of daytime sleepiness, further symptomatic treatment should be considered.

In many conditions, EDS may respond to daytime naps. In narcolepsy, the effects of multiple short naps are well known and studied (for review see [1,2]). In many other conditions, if practically possible, it is worthwhile to evaluate the effect of a planned daytime nap. When limited to, say, 1 hour, there often is no detrimental effect on night-time sleep.

When the aforementioned interventions have been applied and EDS still poses important limitations, symptomatic drug treatment should be considered. Although the available drugs have important drawbacks, the influence of EDS on daytime functioning can be severe, and one should watch for undertreatment.

The objective of any treatment is to eliminate EDS and to produce the fullest possible normal function for patients at work, at school, at home, and socially. Before starting treatment with stimulants, the patient should be informed of their time-limited effect – i.e. relapse into sleepiness once the drug effect has petered out. Any therapy-stabilized patient should be seen by a specialist at least once a year for treatment efficacy, side effects, including night sleep disturbances, mood changes, and cardiovascular or metabolic abnormalities, and also for the development of tolerance. Tolerance can sometimes be avoided by taking drug holidays in periods when perfect wakefulness is not required (e.g. rest regimen in illness) or in days with a different regimen (e.g. no-work days at weekends). Patients who fail to respond to adequate doses of stimulant medication should be carefully reassessed for other sleep disorders that may contribute to EDS.

Individual differences in effectiveness, side effects, and tolerability are large. Therefore, knowledge of effectiveness of a certain stimulant as

assessed in groups is of relative importance when making a choice for an individual. The delayed or immediate action of a drug and its duration of action may be of more importance than the expected effectiveness.

The best-known and most effective compounds to treat EDS remain the amphetamine-like CNS stimulants. The use of the nonamphetamine stimulant modafinil has considerably increased over the last years, however, based on the more favorable side-effect profile and several large controlled trials. Alternative treatment options are limited unfortunately, but include sodium oxybate, monoamine oxidase (MAO) inhibitors, some antidepressants with stimulating properties, or caffeine. Failure of first-line options is one of the reasons to involve a sleep-specialist. Note that none of mentioned drugs is considered safe in pregnancy and during breastfeeding (for review see [3]).

## Indications

Narcolepsy is the “prototype” disorder that is treated with stimulants. Most of the clinical experience is with this disorder, and the same holds true for the (limited) randomized controlled trials. The treatment of narcolepsy and other central hypersomnias is discussed in chapter 19. Although formal data is limited, EDS is often treated when present in neurological disorders. Beneficial effects of modafinil have been reported in myotonic dystrophy (chapter 12), extrapyramidal disorders [4–6] (chapters 9 and 10), multiple sclerosis [7] (chapter 20), and traumatic brain injury [8] (chapter 17). In these forms of secondary EDS, the distinction from fatigue is very important, as this symptom is much less responsive to pharmacological treatment.

## Amphetamine derivatives

### Amphetamines

Amphetamines have been used as a stimulant from the early 20<sup>th</sup> century [1,3,9,10]. There are several compounds in this class that differ in potency, duration of action, and side-effect profile. The mode of action of these drugs is complex, but the central mechanism entails the enhancement of catecholamine release (dopamine and norepinephrine) as well as uptake inhibition. In higher doses, other mechanisms start to play a role, including interaction with monoamine transporters. Because of the side effects and the widespread abuse, amphetamines are less often used nowadays. Methamphetamine is severely restricted for this reason in many countries. Dextroamphetamine is still in relatively common use, however. Typical doses for dextroamphetamine lie between 5 and 60 mg per day. Low doses may be effective, and the drug should always be slowly titrated. Duration of

action is relatively long, in the range of 6–10 hours. Side effects are typically related to alpha-adrenergic stimulation, and include tachycardia and increased blood pressure. Restlessness, irritability, and agitation may occur with long-term use. Psychotic symptoms may also appear, albeit rarely. Amphetamines are not recommended in patients younger than 3 years.

Pemoline has often been used in the past. Although the stimulatory effect is less than the other amphetamines, there is also a milder side-effect profile. However, cases of lethal hepatotoxicity have resulted in its withdrawal from the market in many countries.

### **Methylphenidate**

Methylphenidate is a piperazine derivative of amphetamine, with a comparable mode of action [1,3,9,10,11]. The stimulant efficacy is about the same, if not slightly less than the amphetamines. The most important difference is the duration of action, which is considerably shorter, in the order of 3–4 hours. Together with the rapid onset of effect, it makes methylphenidate suitable for use “on demand,” in situations where sleepiness is likely to cause a problem. Typical doses are in the range 10–60 mg divided over 1–3 times (maximum 20 mg at once). Long-acting methylphenidate is available in some countries. The side-effect profile is comparable to the amphetamines. The safety profile seems better than that of amphetamines, although proper safety studies are lacking. The drug is not recommended in children below 6 years.

### **Modafinil**

Modafinil was developed in France in the 1980s as a stimulant not chemically related to the amphetamines [1,2,12,13,14]. Initially, an alpha-1 agonist action was presumed, but this was questioned later. Recent studies point to an increasing effect on dopamine and norepinephrine signaling, although the exact mechanism of action remains unknown. The starting dose is 200 mg per day, either once in the morning, or divided in two doses. If not efficacious, one should titrate up to 400 mg per day, although higher doses have been reported to have good effects and are well tolerated. The duration of action is relatively long (elimination half-life is 10–15 hours), so one or two doses (in the morning and at noon) typically cover the whole day. Generally speaking, the stimulant effect of modafinil is somewhat less than the amphetamines. On the other hand, side effects are usually mild. The most important undesirable effects include headache, nausea, loss of appetite, and nervousness, but they are infrequent and seldom lead to therapy refusal [15]. Tolerance is not common, although some reports do require increases in doses over time. Modafinil induces P450 activity to some extent, which may require adjustments of other medication, especially oral contraceptives. It is recommended to

reduce the dosage in elderly patients and in hepatic insufficiency. Children between 12 and 18 years can be treated by adequately reduced doses of modafinil.

Armodafinil [2,16] is the recently developed the R-enantiomer of modafinil having longer action and similar efficacy and safety profile. Armodafinil is given in smaller dose than modafinil and only once a day.

## **Other treatment options**

### **Caffeine**

Caffeine acts as a (relatively mild) stimulant, and its usefulness in this respect may be under-recognized in practice [13]. Caffeine is a xanthine derivative, and a nonspecific adenosine receptor antagonist. Adenosine is an interesting neurotransmitter, which levels increase with prolonged wakefulness, and therefore acts as a homeostatically driven “sleep signal.” Caffeine is typically obtained from various drinks, but is also sold over the counter in many countries. Twice daily doses of 100 mg seem to have a rather favorable effect/side-effect ratio.

### **Selegiline**

Selegiline is a potent irreversible MAO-B inhibitor, which is metabolized into various compounds, including amphetamine and methamphetamine [1,2,13]. There have been a number of reports showing a beneficial effect of 10–40 mg of selegiline on EDS in narcolepsy. It can be a useful drug for patients with an insufficient reaction to modafinil who do not tolerate amphetamines well. However, dietary restrictions and incompatibility with triptans and SSRIs limit its routine use.

### **Alerting antidepressants**

These include the dopamine reuptake inhibitor bupropion, and venlafaxine – a combined serotonin-norepinephrine reuptake inhibitor. The drugs have limited stimulating effects, which can still be useful in some cases. However, side effects such as nausea, dry mouth, and other anticholinergic symptoms may limit their use [13].

### **Mazindol**

Mazindol is an imidazoidine derivative that was developed as an appetite suppressant [1,13]. It has a pharmacological profile that is comparable to amphetamines, with rather prominent dopamine and norepinephrine reuptake blocking properties. Typical doses are 2 mg twice daily, to remarkably good effect in some patients. Side effects can be prominent nevertheless, including nervousness, tachycardia, and anorexia. Mazindol

has been taken off the market in many countries because of severe side effects (pulmonal hypertension and valvular regurgitation) in related appetite-suppressing drugs, in particular fenfluramines. Closely monitored treatment with annual cardiac checks including ultrasound may still be useful in those patients with a clear beneficial response.

### Sodium oxybate

Sodium oxybate (gammahydroxybutyrate, 4.5–9 g divided over two night-time doses) reduces EDS in narcolepsy and also in Parkinson's disease [1–3,17,18]. The effect of sodium oxybate on alertness is noticeable within some weeks. The mechanism by which EDS improves is not completely known – it is suggested that the improvement of night sleep quality represents only a part of sodium oxybate action on alertness. Long-term treatment by sodium oxybate is associated with few side effects, but sleepwalking and nocturnal enuresis have been reported. Sodium oxybate should not be used with alcohol or other CNS depressants. Its abuse potential seems mild with appropriate use.

#### Key points

- EDS should be distinguished from fatigue. “Do you fall asleep unintentionally during the day?” is a key question to ask.
- EDS can have severe consequences on daily functioning. Treatment should therefore always be considered.
- Always consider sleep deprivation and/or nocturnal sleep disturbances as a cause of EDS, and treat accordingly.
- Modafinil and methylphenidate are first-line pharmacological treatment options. Modafinil has a favorable side-effect profile, and a relatively long duration of action. Methylphenidate is often more potent, and can be used on an ad-hoc basis.
- Failure of first-line treatment options is an indication to consult a sleep specialist.

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## CHAPTER 7

# Nonpharmacological treatments

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### Introduction

Sleep disorders are a common health problem, particularly in developed countries. Nonpharmacological interventions play a central role in the treatment of many sleep disorders and often represent the treatment of choice. These treatments typically are delivered in the context of a specific sleep disorders clinic. This chapter presents the most common nonpharmacological interventions for the primary categories of sleep disorders: sleep-related breathing disorders, insomnia, and circadian rhythm sleep disorders. The indications, effectiveness, and side effects of each treatment are reviewed.

### Sleep-related breathing disorders

Sleep-related breathing disorders are very common, and usually managed by respiratory physicians. However, they can be associated with specific neurological disorders, such as extrapyramidal or neuromuscular disease (see e.g. chapters 9–13) and are important to recognize.

Obstructive sleep apnea is the commonest significant example of these disorders, with international prevalence estimates ranging from 2–7% of the general population [1]. Apnea is defined as a collapse (either partial or total) of the pharyngeal airway during sleep, causing a cessation in breathing lasting at least 10 seconds [2]. Apneas occur periodically during the sleep episode, causing sleep fragmentation, hypoxemia, hypercapnia, oxyhemoglobin desaturation, and sympathetic activation [3]. Prominent risk factors for sleep apnea include obesity, male gender, excessive alcohol use, advancing age, and certain craniofacial features (e.g. retrognathia,

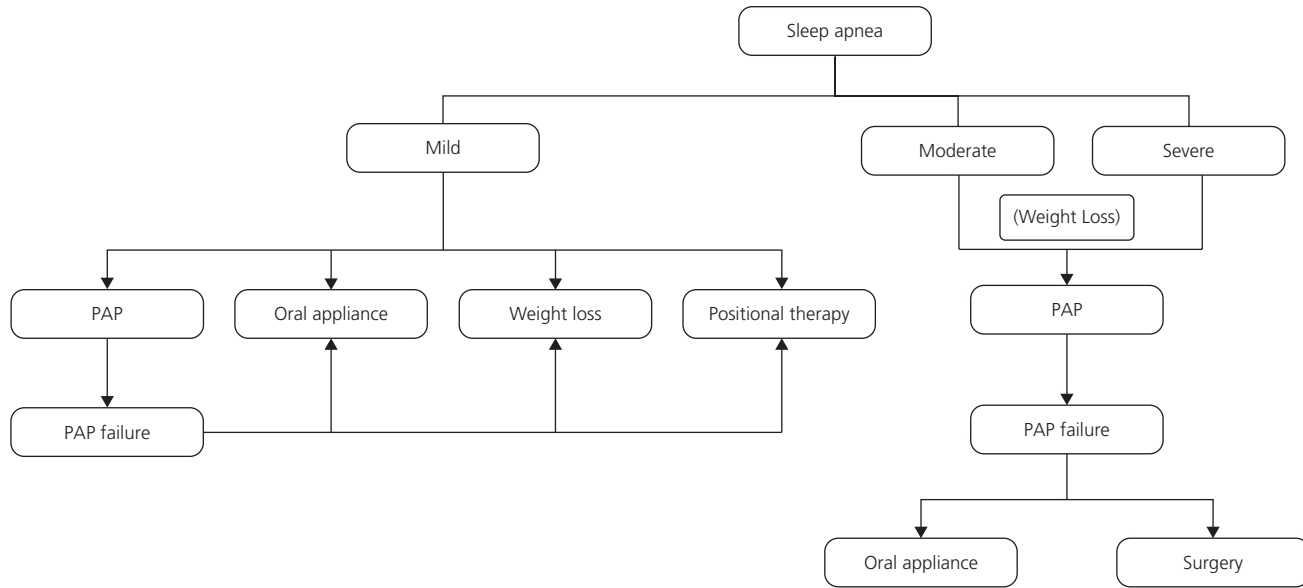
micrognathia, crowded airway) [1]. Sleep apnea is associated with significant cardiovascular morbidity, excessive daytime sleepiness, increased risk of automobile accidents, cognitive difficulties, depression, and impaired glucose metabolism [1,3]. The primary approaches for treating sleep apnea are nonpharmacological and consist of positive airway pressure (PAP) therapies, surgical procedures, and oral appliances (see figure 7.1). Behavioral interventions typically provide adjunctive support in managing the disorder and are rarely used as primary strategies.

### **Positive airway pressure therapies**

Positive airway pressure (PAP) therapy is the treatment of choice for sleep apnea. This treatment consists of a bedside blower unit that delivers an increased pressure of filtered room air to the patient via a nasal or oronasal mask. Positive airway pressure maintains upper airway patency during sleep acting as a pneumatic “splint,” thereby eliminating apneas along with the associated hypoxemia and sleep fragmentation. Positive airway pressure treatment reduces daytime symptoms and cardiovascular risk [4]. In recent years, there have been significant advances in PAP technology. Whereas traditional PAP therapy consists of an unfluctuating flow of continuous air pressure (CPAP), alternative types of pressure delivery, such as bi-level, automatic, and servoventilation systems target a wider range of patients, such as patients with pressure intolerance to standard CPAP or those with certain medical comorbidities (e.g. heart failure, restrictive lung disease) [4]. In addition, a wide variety of mask interfaces can accommodate various patient needs and preferences.

Positive airway pressure therapies are recommended as a primary treatment in sleep apnea and are considered safe and effective [5,6]. Although there are many side effects, most are minor and can be alleviated through close follow-up with a healthcare provider. Common side effects include nasal congestion/obstruction, rhinorrhea, pressure intolerance, claustrophobia, difficulties with mask interface (e.g. skin irritation or allergy, air leaks) and social factors (e.g. embarrassment, intolerance by bed partner) [4,5]. Tinnitus, aerophagia, pneumoencephalus, and pneumothorax have been reported but are rare. Contraindications to PAP therapies may include recurrent sinusitis and, for oronasal masks, uncontrolled acid reflux or vomiting.

Despite the efficacy of PAP therapies, the overall success of this treatment is limited by patient acceptance and adherence. On average, 20% of patients reject PAP therapy initially, and up to 25% who begin treatment discontinue it within the first few years [7]. Most patients fall short of using their devices nightly for their entire sleep period. Research has not elucidated consistent predictors of adherence, although problems often arise within the first weeks of treatment and may be related to side effects, low motivation, or inadequate patient education.



**Figure 7.1** Decision tree for the treatment of sleep apnea. For details on individual treatment options, see text.

## **Surgical interventions**

The goal of surgery for sleep apnea is to reduce or eliminate airway obstruction by removing excess tissue or altering airway anatomy [8]. There are a variety of surgical interventions, from outpatient laser procedures to major craniofacial surgeries, modifying soft tissue [e.g. uvulopalatopharyngoplasty (UPPP), radiofrequency ablation, adenotonsillectomy] or bony structures (e.g. maxillomandibular advancement, genioglossus advancement, hyoid suspension). Tracheostomy successfully bypasses airway obstruction but is rarely performed; it is predominantly used in severe and/or emergency cases when PAP therapy is not feasible. Another indication for tracheostomy is nocturnal stridor in patients with multiple system atrophy, when this does not respond to PAP treatment (see chapter 10).

The selection of surgical procedure is individualized to the patient. A comprehensive preoperative assessment is essential in determining the site of obstruction as the target for surgery. Surgical candidates include patients with no major medical comorbidities who fail or reject PAP therapy, have nasal obstruction, or have significant anatomical deformities or features that narrow the airway (e.g. micrognathia, retrognathia, tonsillar hypertrophy) [8].

The success of sleep apnea surgery is clouded by a lack of standardization in defining successful outcomes and a paucity of rigorous scientific evidence. Some of the more common procedures such as UPPP have a success rate of less than 50%, with long-term benefits diminished by weight gain [8]. Some patients who elect for surgery in hopes of avoiding PAP therapy must eventually return to using their PAP device. Side effects and complications are those anticipated with surgery, in addition to postoperative pain, velopharyngeal stenosis or insufficiency, dysphagia, dry throat, speech difficulties, and facial/dental injury or numbness [8].

## **Oral appliances**

Oral appliances (OAs) include a wide range of dental devices worn during sleep that share the common goal of manipulating the upper airway anatomy to increase oropharyngeal space and/or decrease collapsibility, thereby reducing or eliminating sleep-disordered breathing [9]. Mandibular repositioning devices are the most common type of oral appliance and work by advancing the mandible anteriorly. Whether prefabricated (e.g. “boil and bite”) or custom made, oral appliances require fitting, adjustment, and monitoring by a dental expert with specialized training in treating sleep-disordered breathing. Once final adjustments are made, follow-up testing is recommended to ensure effectiveness [10].

Oral appliances are primarily recommended for patients with mild to moderate sleep apnea and may be a reasonable treatment option for patients who reject or fail PAP therapy [10]. Contraindications to the use of oral appliances may include inadequate dentition, periodontal disease, temporomandibular joint disorder, or bruxism [9]. Side effects are generally mild and transient, but may lead to treatment discontinuation in some individuals. Commonly reported side effects are pain or discomfort (temporomandibular, myofacial, or dental), dry mouth, excessive salivation, tooth movement, or occlusal misalignment [9,10].

Oral appliances are a successful treatment for approximately half of patients [9]. The effectiveness of this therapy diminishes with increasing severity of apnea (and increasing body mass index), such that the use of oral appliances is not recommended as a first-line treatment in patients with severe sleep apnea [9,10]. Compared to other treatments for sleep apnea, oral appliances are not as efficacious as PAP therapy in reducing apnea symptoms but may be preferred by patients [9,10]. Similar to PAP therapy, adherence to treatment may be problematic; at one year post-treatment median adherence to oral appliances is 77% and tends to decrease over time [9,10]. The success of mandibular repositioning devices compares favorably to UPPP and also may be the most effective device in comparison to other oral appliances [9,10].

## **Behavioral management of sleep-related breathing disorders**

### **Sleep position therapies**

In more than half of sleep apnea patients, the severity of sleep apnea is exacerbated while in the supine position [11]. In some cases, apnea may be completely resolved by avoiding this position. Sleep position therapies consist of a handful of strategies designed to prevent sleep in a supine position via the use of positional alarms or specially designed pillows or bed clothes [11,12]. These therapies are usually recommended as a secondary or supplemental treatment strategy for sleep apnea [12]. Although preliminary findings support their effectiveness, such strategies have generally not been evaluated in large, randomized controlled trials.

### **Lifestyle factors**

Lifestyle modifications such as weight reduction, smoking cessation, and avoidance of respiratory depressants including excessive alcohol, are important factors for successful management of sleep apnea. Weight loss in obese individuals with sleep apnea, either through dietary modification or bariatric surgery, can reduce the severity of the sleep apnea, lower effective PAP pressure, and improve comorbid medical conditions [8,12].

## **Insomnia**

Similar to sleep apnea, insomnia is a highly prevalent and significant health concern, with over 10% of the population meeting diagnostic criteria [13,14]. Behavioral therapies for insomnia discussed in this section target the underlying mechanisms that may perpetuate a chronic insomnia complaint, such as conditioned arousal at bedtime, unhelpful or distorted beliefs and attitudes about sleep, or excessive time spent in bed. These therapies are typically delivered over a series of sessions by psychologists or other healthcare providers with specialized training in behavioral sleep medicine.

### **Sleep restriction therapy**

Individuals who experience difficulty falling or staying asleep may seek to maximize their opportunity to sleep by spending excessive time in bed. Unfortunately, this practice leads to increased time spent awake each night and may even serve to perpetuate an insomnia problem by further fragmenting the sleep-wake pattern. Sleep restriction therapy restricts a patient's time in bed to more closely match his or her actual sleep requirement [15]. Creating a state of mild sleep deprivation increases sleep drive. Eliminating time spent awake in bed during the night also serves to improve sleep efficiency and consolidate the sleep pattern. For this intervention, maximum allowable time-in-bed is prescribed based upon a patient's average total sleep time, as determined from daily sleep logs. In subsequent sessions, the time-in-bed prescription is adjusted depending on the therapeutic response.

### **Stimulus control**

Stimulus control therapy for insomnia is designed to target the conditioned arousal at bedtime that may occur through the repeated association of the bed and bedroom with unsuccessful sleep attempts [16]. Treatment strategies seek to re-associate the sleep environment with successful sleep attempts by limiting activities incompatible with sleep and by establishing a consistent sleep-wake schedule. Standard stimulus control recommendations are as follows: go to bed only when sleepy, establish a standard wake-up time 7 days a week, get out of bed when unable to sleep for more than 20 minutes, avoid certain behaviors in the bedroom (e.g. reading, watching TV, eating, worrying).

### **Sleep hygiene education and lifestyle factors**

Sleep hygiene education refers to a set of treatment recommendations targeting lifestyle and environmental factors that may influence sleep [17]. Specific sleep hygiene recommendations vary but usually

include education about diet and lifestyle changes that may be beneficial for sleep. Dietary recommendations may include the following: limiting or eliminating use of caffeine, alcohol, and nicotine, avoiding large meals close to bedtime, and eating a protein-rich bedtime snack. Exercise is often recommended for individuals with insomnia as part of sleep hygiene education, although strenuous exercise close to bedtime may have a sleep-disruptive effect. Additional sleep hygiene recommendations are targeted toward establishing environmental conditions conducive to sleep, including scheduling quiet time before bed and controlling ambient noise, light, and temperature.

### **Cognitive therapy**

Cognitive therapy techniques address the cognitive arousal and anxiety associated with insomnia. Patients with chronic insomnia often endorse unrealistic beliefs and attitudes about sleep as well as misconceptions or misattributions regarding the causes and consequences of insomnia [14]. Cognitive therapists use an approach developed for the treatment of depression [18] to assist patients in identifying, challenging, and restructuring dysfunctional beliefs regarding insomnia and its impact.

### **Cognitive behavior therapy**

The most common nonpharmacological treatment for insomnia is a multicomponent approach called cognitive behavior therapy for insomnia (CBTI). CBTI includes components of some or all of the aforementioned behavioral interventions for insomnia (sleep restriction, stimulus control, sleep hygiene education, cognitive therapy, and relaxation therapies) [19,20]. An advantage of CBTI is that it addresses the full range of cognitive and behavioral mechanisms that may perpetuate insomnia.

## **Circadian rhythm sleep disorders**

Circadian rhythm sleep disorders are characterized by disturbances in the timing of sleep and wakefulness, either because of exogenous factors (e.g. shift work or travel across time zones) or because of alterations in the endogenous circadian system. Delayed sleep phase syndrome (DSPS) is the most common circadian rhythm sleep disorder diagnosis in the sleep clinic setting, accounting for 6.7–16% of patients with a complaint of insomnia [21]. DSPS is characterized by a sleep schedule substantially later than conventional sleep onset and rising times; patients typically present with sleep onset difficulties as well as trouble waking up sufficiently early in the morning to meet social or work obligations. Less frequent is advanced sleep phase syndrome (ASPS), characterized



by sleep onset and rising times that are significantly earlier than desired. Both DSPS and ASPS are conceptualized as disorders of the endogenous circadian system; however, behavioral factors (e.g. variability in bed-times and rising times) may contribute to the circadian pacemaker being “out of sync” with the desired schedule [22]. The goal of treatment is to resynchronize circadian functioning with the 24-hour light/dark cycle and is achieved through phototherapy, chronotherapy, and/or melatonin administration.

### **Phototherapy**

Bright light administration, or phototherapy, has a strong phase-shifting effect on the endogenous circadian system. Light receptors in the retina connect to the circadian oscillator in the suprachiasmatic nucleus via the retinohypothalamic tract [21]. Bright light stimulation can advance or delay circadian rhythms, depending on the timing of administration in relation to the core body temperature nadir. In DSPS, bright light (at an intensity similar to outdoor daylight) is administered via a light box or visor hat in the morning to advance the circadian phase, whereas in ASPS, it is administered in the early evening [23].

In clinical trials, light exposure has been shown to advance sleep onset time and improve daytime alertness in patients with DSPS and to delay circadian phase and improve sleep quality in patients with ASPS [24]. However, the optimal dose, timing, and duration of phototherapy for circadian rhythm sleep disorders remain unknown [24]. Phototherapy is contraindicated for patients with retinopathy; patients with other eye conditions, such as cataracts or glaucoma, should be monitored by an ophthalmologist while undergoing bright light therapy [23]. Bright light exposure can also interact with certain photosensitizing medications [23]. Other side effects may include irritability, headache, nausea, and hypomania; light therapy may trigger episodes of mania in patients with bipolar disorder [23].

### **Chronotherapy**

Chronotherapy, or prescribed sleep scheduling, consists of progressively delaying or advancing bedtime by 3 hours each day until the desired sleep-wake schedule is reached [21,22]. Once reached, the sleep schedule must be strictly followed in order to prevent a return of symptoms. Although case reports have suggested a role of chronotherapy in ASPS, it is primarily recommended for use in DSPS [24]. Chronotherapy for DSPS takes advantage of the endogenous tendency toward phase delay by prescribing a progressively later bedtime.

In practice, chronotherapy is a challenging treatment for patients, and adherence can be problematic. There have been no controlled studies

and thus treatment efficacy and safety have not been established [24]. Side effects are unknown, but in theory could include increased daytime sleepiness during the treatment phase. Therefore, chronotherapy should be carried out by a sleep specialist experienced with circadian rhythm disorders.

### Key points

- Nonpharmacological interventions play a major role in treating sleep disorders.
- Positive airway pressure therapies are the primary treatment for sleep apnea, with oral appliances and surgical interventions offering additional options.
- Behavior therapies are effective in treating primary insomnia, and possibly more effective than drugs.
- Besides the use of timed melatonin, patients with circadian rhythm sleep disorders may benefit from phototherapy and chronotherapy.
- The above interventions typically require referral to providers specializing in sleep medicine.

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**PART III**

Movement and  
Neurodegenerative  
Disorders

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## CHAPTER 8

# Restless legs syndrome and periodic limb movement disorder

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### Introduction

Although widely varying in its severity, proactive questioning reveals that restless legs syndrome (RLS) is a very common phenomenon in a variety of populations. A term coined by Ekbom in 1945 [1], RLS is characterized by an imperative desire to move the extremities, usually the legs, most often in association with unpleasant sensory phenomena. Relaxation or inactivity specifically worsens the symptoms whereas movement or vigorous rubbing relieves them, if only temporarily.

A key feature is that symptoms are worse or occur uniquely in the late evening and night, often disrupting nocturnal sleep with subsequent significant daytime consequences [2]. Nocturnal sleep can additionally be disrupted by associated periodic limb movements (PLMs) which commonly coexist with RLS. PLMs are repetitive, usually stereotyped leg movements, most often bilateral, that resemble a slow version of the peripheral withdrawal reflex. In periodic limb movement disorder (PLMD), by definition, there needs to be a clinical consequence on sleep quality or daytime wakefulness caused by the leg movements, not attributable to any other sleep disorder. As such, it is often debated whether PLMD should be better assessed by movement disorder or sleep specialists. Indeed, the ICSD-2 manual categorizes both RLS and PLMD as “sleep-related movement disorders” [2]. In any event, in the sleep clinic, it is not uncommon to diagnose PLMD in the absence of a clear history of abnormal leg movements or, indeed, with the condition never having been previously considered.

In the early 1980s, Coleman [3] was the first to propose standardized scoring criteria for PLMs that were modified by the American Sleep Disorders Association (ASDA) in 1993 [4] and codified in the ICSD-2 [2].

Recently, new standards for recording and scoring PLMs were proposed by the World Association of Sleep Medicine (WASM) [5]. Whether PLMD in a relatively pure form represents a single disease entity or is part of the phenotypic spectrum of RLS remains a matter of controversy and debate.

## Clinical epidemiology

Population-based surveys using standardized diagnostic criteria have consistently shown that between 5% and 10% of the general population in various parts of Europe and North America have the cardinal and defining symptoms of RLS [6]. Females are twice as likely to be affected. Interestingly, about 20% to 30% of females will experience RLS to varying degrees during pregnancy. The lack of recognition of RLS by primary care physicians as an identifiable and treatable phenomenon undoubtedly leads to underdiagnosis. Many patients, particularly, but not always, at the mild end of the spectrum also fail to seek medical advice. In elderly populations, comorbid conditions and polypharmacy may confuse accurate diagnosis. Conversely, although prevalence studies suggest low rates in children, RLS certainly exists and may account for symptoms wrongly attributed to “growing pains” or attention deficit hyperactivity disorder.

Problematically, PLMs are a common investigative finding even in the absence of complaints of sleep disruption, particularly in the elderly. A PLM index  $>5$  (which is arbitrarily regarded as abnormal) can be found in up to 45% of subjects older than 60 years [7]. Periodic limb movements are also found, possibly incidentally, in a large variety of sleep disorders including insomnia, sleep apnea, narcolepsy, parkinsonism, and REM sleep behavior disorder. However, the association is particularly tight in patients with RLS (a PLM index  $>5$  is present in 80–90% of RLS patients). Although PLMs are common, PLMD, namely, PLMs with symptomatic sleep disruption, is thought to be relatively rare. A large-scale study using a telephone interview and the ICSD criteria from 1990 established prevalence rates of 3.9% in a random multinational population sample [8].

## Clinical aspects

In 1995, the International RLS Study Group developed standardized criteria for the diagnosis of RLS which have been recently modified [9] and included into the ICSD-2 criteria [2]. Four criteria based purely on history are essential to establish the diagnosis of RLS although supportive and associated clinical features may aid diagnosis (table 8.1). The onset of RLS symptoms often follows a fluctuating course with periods of improvement



**Table 8.1** Criteria for restless legs syndrome [9]

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<i>Essential diagnostic criteria for restless legs syndrome</i>	
1	An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2	The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3	The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4	The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)
<i>Supportive clinical features</i>	
Family history	The prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS
Response to dopaminergic therapy	Nearly all people with RLS show at least an initial positive therapeutic response to either levodopa or a dopamine-receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson's disease. This initial response is not, however, universally maintained
Periodic limb movements	Periodic limb movements in sleep occur in at least 85% of people with RLS; however, they also commonly occur in other disorders and in the elderly. PLMs are much less common in children than in adults

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or remission over a period of weeks, months, or even years. The precise expression of symptoms varies widely from patient to patient. Overall, however, the frequency and severity of symptoms tend to progress with age and permanent remissions are considered rare. To assess the severity of symptoms and to monitor treatment outcome, the International RLS Study Group rating scale for RLS may be applied [9,10].

Restless legs syndrome is usually divided into idiopathic (primary) and symptomatic (secondary) forms although the clinical presentation is identical. Approximately 50% of the patients with the idiopathic form report a positive family history with at least one first-degree relative affected with RLS. Typically, patients with a positive family history have a much younger age of onset and there is sometimes a suggestion of "anticipation" with an earlier onset in subsequent generations. Large pedigrees with familial RLS suggest a strong genetic contribution to RLS.

There are many potential causes or contributors to secondary RLS and clinical examination may reveal abnormalities, in contrast to idiopathic RLS. The commonest associations are pregnancy, especially in the later trimesters with complete relief of symptoms after delivery; iron deficiency; and end-stage renal disease. At least 20% to 30% of uremic patients meet the clinical criteria for the diagnosis of RLS. In addition, peripheral neuropathies (even if subclinical), radiculopathies, rheumatoid arthritis, and Isaac syndrome have all been identified as provoking disorders for RLS. It remains debatable whether Parkinson's disease is an independent RLS risk factor although RLS is undoubtedly quite common in this patient group. Finally, it is important to consider that certain drugs including dopamine D2 receptor blocking agents and many antidepressants can evoke or, at least, worsen RLS and PLMD.

In PLMD, although PLMs may be associated with an EEG arousal or a brief awakening (see figure 8.1), subjects are often unaware of excessive



**Figure 8.1** This 90 seconds epoch of a nocturnal polysomnography of a patient with periodic limb movement disorder contains 7 periodic leg movements during sleep. The overall PLMs index was 48/h. The PLMs (in this epoch only present in the right leg) occur every 10 to 15 seconds during sleep stage 2. Each leg movement is associated with an EEG arousal. From top to bottom: 2 electrooculography (EOG) channels, 3 electroencephalography (EEG) channels, 1 chin electromyography (EMG) channel, electrocardiography (ECG), 8 EEG channels, airflow, respiratory movements of the thorax and abdomen, snoring sound recording, right and left leg EMG of the tibialis anterior muscle, and right and left EMG of the extensor digitorum muscle.

limb movements or even sleep disruption and it is the observation of the bed partner that suggests their presence.

## Diagnostic procedures

Restless legs syndrome is a clinical diagnosis based on history alone. However, investigations are often appropriate to exclude secondary causes and to differentiate RLS from similar disorders that may mimic elements of RLS. Table 8.2 outlines a suggested scheme for investigations. If a peripheral neuropathy is suspected from history or clinical findings such as areflexia, nerve conduction studies may be worthwhile and a search for treatable underlying causes appropriate. Full polysomnography is rarely needed and has little use in diagnosing RLS. However, it can be useful in quantifying the severity and extent of associated PLMs in the context of RLS or PLMD and their disruptive effects on sleep architecture.

The diagnosis of PLMD ideally requires objective measurement of PLMs by nocturnal polysomnography, or actigraphy if there is sufficient expertise for confident interpretation of the data. The diagnostic criteria for PLMD according to the ICSD-2 [2] are summarized in table 8.3. The differential diagnosis of PLMD includes other involuntary movements occurring during sleep such as normal phenomena at the sleep-wake transition (e.g. hypnic jerks), as well as sleep-related epilepsy, propriospinal myoclonus, REM sleep behavior disorder, rhythmic movement disorders of sleep, or nocturnal paroxysmal dystonia. In addition, sleep-related breathing disorders and associated general restlessness following apnea-related arousals may mimic PLMD. For such differentiation, full polysomnography including video monitoring may be needed.

A number of conditions other than RLS must be considered in the differential diagnosis of altered sensations in the legs with positive sensory phenomena. These include disorders of the peripheral nervous system such as small fiber sensory neuropathies and syndromes reflecting irritation or compression of peripheral nerves. Nocturnal leg cramps, “painful legs and moving toes,” and vascular insufficiency can occasionally be mistaken for RLS. Altered lower limb sensations and motor restlessness are

**Table 8.2** Clinical testing for restless legs syndrome

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Tests considered mandatory: hemoglobin, urea, creatinine and electrolytes, serum ferritin
Tests occasional helpful if clinical pointers: thyroid function tests, glucose, B12 and folate levels, nerve conduction studies
Tests rarely helpful unless clear indication or diagnostic confusion: Cerebrospinal fluid analysis for inflammatory markers, video-polysomnography, actigraphy

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**Table 8.3** Diagnostic criteria for periodic limb movement disorder [2]

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- A** Polysomnography demonstrates repetitive, highly stereotyped, limb movements that are:
- 0.5 to 5 seconds in duration
  - Of amplitude greater than or equal to 25% of toe dorsiflexion during calibration
  - In a sequence of 4 or more movements
  - Separated by an interval of more than 5 seconds (from limb-movement onset to limb-movement onset) and less than 90 seconds (typically there is an interval of 20 to 40 seconds)
- B** The PLM index\* exceeds 5 per hour in children and 15 per hour in most adult cases
- C** There is clinical sleep disturbance\*\* or a complaint of daytime fatigue
- D** The PLMs are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder
- 

\*The PLM index must be interpreted in the context of a patient's sleep-related complaint. In adults, normative values higher than the previously accepted value of 5 per hour have been found in studies that did not exclude respiratory event-related arousals (using sensitive respiratory monitoring) and other causes for PLMs. New data suggest a partial overlap of PLM index values between symptomatic and asymptomatic individuals, emphasizing the importance of clinical context over an absolute cut-off value.

\*\*If PLMs are present without clinical sleep disturbance, the PLMs can be noted as a polysomnographic finding, but criteria are not met for a diagnosis of PLMD.

also reported in patients with general anxiety disorders and attention deficit hyperactivity disorder. Akathisia in association with antipsychotic medication may superficially resemble RLS but there is no reported urge to move the legs in such patients. Furthermore, any witnessed movements tend to be continuous and are relatively un concerning to the subject.

Given the improvement of RLS symptoms in some patients with a single dose of a dopaminergic agent such as levodopa, some authorities advocate that a drug challenge can be used to help diagnosis. It is claimed to have a high sensitivity and specificity in subjects with RLS and is considered as a supportive feature although is not a widespread practice [11].

## Management

### General aspects

The decision to start treatment should always depend on an individual's severity and frequency of symptoms and the degree to which they interfere both with daily activities and nocturnal sleep. Clearly if an underlying potentially treatable cause is revealed, specific therapies such as iron replacement are appropriate. Most authorities recommend an empirical trial of iron replacement if ferritin levels are under 45 mg/l even in the absence of anemia. Folic acid replacement has also been shown to be of benefit in pregnancy or, obviously, in folic acid deficiency.

Nonpharmacological treatment may consist of specific physical strategies such as moving the legs in certain patterns or applying various sensory stimuli. This approach rarely helps significantly if symptoms are moderately severe. Similarly, recommended modifications of lifestyle such as limiting alcohol and avoiding nicotine or caffeine rarely improve the situation for any length of time.

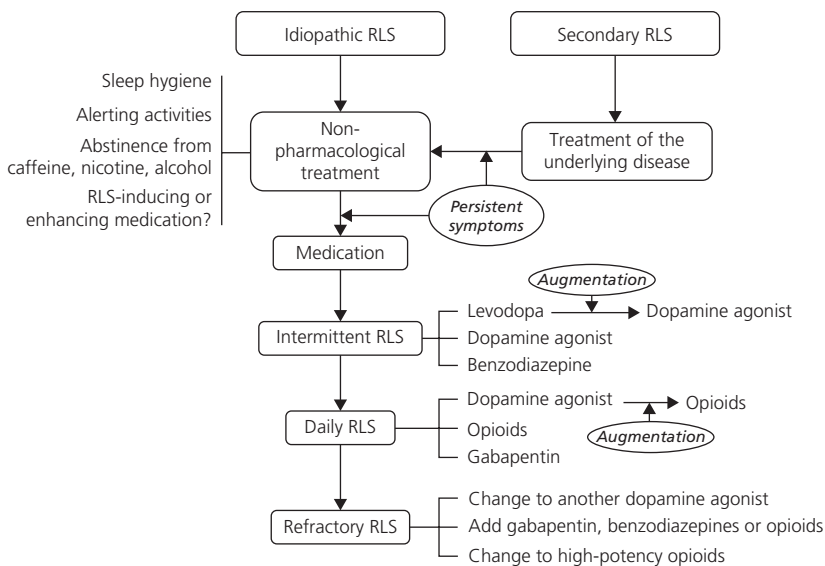
Pharmacological agents are often needed for adequate symptom control in RLS and, more controversially, PLMD. Effective treatments have been demonstrated in a number of large-scale multicenter trials over the last few years. A treatment flowchart is given in figure 8.2. Dopaminergic drugs, including levodopa and dopamine agonists, are currently regarded as the first-line treatment option in moderate to severe RLS.

Therapy of PLMD, if indicated, is assumed to be similar to the treatment of RLS, although there are insufficient treatment trials specifically targeting PLMD (for review see [12]).

## Dopaminergic agents

### Levodopa

Evidence-based guidelines have identified levodopa as effective in the treatment of RLS [13]. Levodopa plus a decarboxylase inhibitor (carbidopa or benserazide) generally results in robust initial relief with the first dose. Controlled studies have shown the efficacy of levodopa both in idiopathic and uremic RLS. In subsequent comparative studies, levodopa was found to be effective in reducing RLS, but was inferior to ropinirole and pergolide



**Figure 8.2** Treatment flowchart for restless legs syndrome.

in that respect. Adverse events may include dry mouth, nausea, vomiting, headache or drug-induced insomnia, and sleep disruption, especially in the elderly. Early morning rebound of symptoms may occur, necessitating a second dosing during the night or the prescription of a sustained-release formula. Thus, levodopa can be recommended for patients with intermittent but not daily RLS.

### Dopamine agonists

Dopamine agonists are regarded as first-line treatment for moderate to severe primary RLS, especially if daily treatment is required. This is due to their well-documented effectiveness and overall good tolerability (for review see [14]). The available dopamine agonists differ considerably with respect to pharmacokinetics (e.g. half-life), dopamine receptor profiles, potential serious side effects, availability of long-term experience, and licensing status (table 8.4). If ergot derivatives (pergolide and cabergoline) are being considered, there is a need to increase the dosage slowly to avoid side effects, making these drugs less suitable to use on an intermittent basis.

**Table 8.4** Dopamine agonists for the treatment of restless legs syndrome

		Receptor subtype	Half-life (h)	Starting dose (mg)	Daily dose range (mg)	Common side effects
Non-ergot	Ropinirole	D2/D3	~ 6	0.25	1–4	Nausea; headache; fatigue; vomiting
	Pramipexole	D2/D3	8–12	0.125	0.375–1.5	Similar to ropinirole
	Rotigotine	D1/D2/D3	3–7	1	1–3	Application site reactions: erythema, rash, irritation, inflammation; nausea; drowsiness; headache
Ergot	Pergolide	D1/D2	16–24	0.05	0.25–0.75	Nausea; vomiting; headache; rhinitis; insomnia; dizziness
	Cabergoline	D2	~ 65	0.5	1–4	Similar to pergolide

Concerns regarding the development of “sleep attacks,” following observations in parkinsonian patients started on low-dose dopamine agonists, do not seem to be a major concern in RLS. However, although probably more common in levodopa treatment, long-term studies suggest that augmentation may also occur with most of the dopamine agonists.

### **Non-ergot derivatives**

Several placebo-controlled and open-label studies have shown that ropinirole is effective in significantly improving both the subjective of RLS and objective measurements of its consequences for periods up to 52 weeks (for an overview of treatment studies see [15]). Ropinirole is generally well tolerated with early response to treatment initiation at first dose. Ropinirole is usually started at 0.25 mg although most cases require around 2 mg with maximum doses in individual patients of up to 4 mg (table 8.4).

Pramipexole has also been shown to be effective in reducing sensory restless legs symptoms and PLMs in controlled and open-label trials for time spans between one night and several months (review in [16]). Titration of pramipexole is usually started at 0.125 mg and increased every few days. In most cases, daily pramipexole doses will be below 1.0 mg, often 0.5 mg and less.

Rotigotine is designed to be administered as a transdermal patch for 24 hours continuous dopaminergic stimulation. A recent multicenter controlled study has shown that rotigotine applied once a day for 6 months (dose range 1–3 mg over 24 h) significantly relieved the night- and day-time symptoms of idiopathic RLS. Application site reactions were the most common adverse events [17] (table 8.4) in comparison to oral agonists in which nausea can be a significant and limiting side effect.

### **Ergot derivatives**

Although both pergolide and cabergoline have proven efficacy in reducing sensory RLS symptoms and PLMs both at sleep onset and during the night in placebo-controlled trials, they are rarely used in current practice. This is mostly due to concerns over potentially serious long-term side effects such as cardiac valvulopathies, constrictive pericarditis, and pleuropulmonary fibrosis. These problems have been well documented in Parkinson's disease treated with pergolide and cabergoline. Given the relative safety of non-ergot compounds, it is rarely appropriate to use pergolide or cabergoline in nonprogressive, relatively benign conditions such as RLS or PLMD.

### **Augmentation**

All dopaminergic agents, however, have the potential for causing “augmentation” of RLS symptoms in which restlessness and associated sensory phenomena occur earlier in the day, often in a more severe form

**Table 8.5** Key features of augmentation [18]

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A or B and C for at least 1 week and a minimum of 5 days per week	
<b>A</b>	Shifting of RLS symptoms to a period of time 2 h earlier than was the typical period of daily onset of symptoms before pharmacological intervention
<b>B</b>	Two or more of the following features: <ul style="list-style-type: none"> <li>• An increased overall intensity of the urge to move or sensation that is temporally related to an increase in daily medication dosage</li> <li>• A decreased overall intensity of the urge to move or sensation that is temporally related to a decrease in the daily medication dosage</li> <li>• The latency to RLS symptoms at rest is shorter than the latency with initial therapeutic response or before treatment</li> <li>• The urge to move or sensations are extended to previously unaffected limbs or body parts</li> <li>• The duration of treatment effect is shorter than the duration with initial therapeutic response</li> <li>• Periodic limb movements while awake either occur for the first time or are worse than with initial therapeutic response or before treatment</li> </ul>
<b>C</b>	No other medical, psychiatric, behavior, or pharmacological factors explain the exacerbation of RLS

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involving additional body parts such as the arms. A detailed description of key features of augmentation according to a WASM consensus report [18] is given in table 8.5. Augmentation may develop as early as during the first month and in up to 82% of patients [19]. The occurrence typically correlates with higher daily doses (e.g. levodopa >300 mg). In terms of newer dopamine receptor agonists (pramipexole, ropinirole, rotigotine) augmentation may also occur, but probably less frequently. As a consequence of augmentation, it may be necessary to lower the dosage, adjust the timing or even withdraw a previously successful drug and switch to other agents.

## Opioids

Opioids are generally considered as a second-line treatment of RLS. They are recommended if symptoms fail to respond to dopaminergic medication or in cases where tolerance or augmentation are major issues. Tilidine, tramadol, oxycodone, and methadone are successfully used in clinical practice although a number of patients take codeine bought from retail pharmacies as a nonprescribed drug (table 8.6). Side effects include dizziness, sedation, constipation, nocturnal confusion, and worsening or even the development of sleep-related breathing disorders. Dependency does not seem to be a major risk of long-term administration [20]). It is likely that opioids are underused by clinicians and, perhaps in combination with dopaminergic agents, will often improve symptom relief further in patients at the severe end of the RLS spectrum.



**Table 8.6** Opioids for the treatment of restless legs syndrome

Agent	Initial dose	Usual daily dose range	Common adverse effects
Tilidine/Naloxone	50/4 mg	50/4 mg–200/8 mg	Nausea, sedation
Tilidine/Naloxone controlled release	50/4 mg	50/4 mg–200/16 mg	Nocturnal confusion
Tramadol	50 mg	50–300 mg	Similar to tilidine
Methadone	5 mg	5–40 mg	Similar to tilidine
Propoxyphene	65 mg	100–500 mg	Nausea, constipation, nocturnal confusion
Oxycodone	5 mg	5–20 mg	Similar to propoxyphene
Dihydrocodeine (DHC)	30 mg	60–120 mg	Similar to propoxyphene

### Gabapentin and other anticonvulsants

Despite the lack of controlled evidence, drugs such as gabapentin or pregabalin may sometimes be considered as a drug of first line, particularly in patients with prominent unpleasant or frankly painful sensory symptoms. These drugs may also directly enhance deep slow-wave sleep which is characteristically deficient in RLS and PLMD. Combination with drugs mentioned previously such as dopamine agonists can be a useful strategy.

In idiopathic RLS, subjective relief of RLS symptoms has also been demonstrated with valproic acid, but the number of PLMs did not change. Carbamazepine may ameliorate subjective symptoms, but, again, recorded PLMs remain unchanged (review in [21]).

### Benzodiazepines and other hypnotics

Clonazepam is regarded as an alternative treatment strategy in RLS and PLMD and is used to improve sleep continuity in a relatively nonspecific manner. Again, combination treatment options that include clonazepam may suit individual patients. In severe sleep-onset insomnia or sleep fragmentation, the shorter-acting hypnotics such as zopiclone, zolpidem, or zaleplon may be helpful, usually on an intermittent basis [22].

### Iron

Because iron deficiency is common in RLS, oral iron supplementation is an established treatment. Ferrous sulfate (325 mg) given with vitamin C three times daily is the recommended regimen, if gastrointestinal discomfort is tolerated. Magnesium supplementation may show beneficial effects in mildly affected RLS patients with a postulated magnesium deficiency.

**Key points**

- Restless legs syndrome is a common and underdiagnosed condition with a wide spectrum of severity.
- In the diagnostic work-up, it is important to search for potentially treatable causes for secondary RLS, such as iron deficiency.
- Periodic limb movements are very often present in patients with RLS but their clinical relevance is often unclear.
- When moderate or severe, RLS is a treatable condition and dopamine agonists are regarded as first-line therapy.
- Augmentation is an important “side-effect” of dopaminergic agents, and sometimes difficult to treat.
- Opioid drugs are useful as second-line therapy, often in combination with dopaminergic supplementation.
- If sensory symptoms predominate, anecdotal evidence suggests that pregabalin or gabapentin are helpful.

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## CHAPTER 9

# Sleep disorders in idiopathic Parkinson's disease

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## Introduction

Over the last two decades, the notion that idiopathic Parkinson's disease is predominantly a motor disorder simply reflecting nigrostriatal dopamine deficiency has been increasingly revised. As the disease advances, the nonmotor aspects of Parkinson's disease are now considered at least as disabling as the more obvious motor deficits and are generally more difficult to manage. Alongside the well-established cognitive, neuropsychiatric, and autonomic problems seen in Parkinson's disease, significant sleep-related symptoms are now routinely assessed and sometimes treated. Although severe sleep disturbance is seen as a relatively new element to the spectrum of possible symptoms in Parkinson's disease, it is interesting to acknowledge that James Parkinson himself was aware that patients were often "constantly sleepy" and "exhausted."

The whole gamut of sleep disorders may be seen in Parkinson's disease, occasionally in the same patient. Insomnia, particularly the inability to maintain the state of sleep, is extremely common. There are numerous potential causes for poor-quality nocturnal sleep in Parkinson's disease including significant difficulties in moving around the bed during nocturnal awakenings. Daytime sleepiness, in part a result of poor overnight sleep, but mainly caused by the underlying neurodegenerative process, is also prevalent although may not be reported by patients who often seem unaware of the extent of their somnolence. Finally, nocturnal disturbances such as parasomnias, particularly from REM sleep, and prolonged

confusional episodes are also a significant issue for many patients and carers alike.

Because of the potential complexity of sleep-wake problems in Parkinson's disease, it is difficult to define a typical symptom profile or, indeed, to construct simple protocols and guidelines for management. A further confound is that conventional Parkinson's disease drug treatment may fuel or even cause sleep-related symptoms. In reaching diagnostic conclusions, assuming a detailed history is available, it is debatable what further useful information is gained from detailed sleep investigations other than clarifying the severity of the problem. Despite these caveats, it is argued that treatment options will exist for the vast majority of Parkinson's disease patients with sleep-related symptoms. However, treatments need to be tailored to individual patients and an empirical approach is often necessary, in the absence of formal evidence-based trial data.

## Clinical epidemiology

Every study addressing the issue has confirmed that sleep disorders are highly frequent and disturbing to patients with Parkinson's disease and their carers. In a community-based survey, 60% of patients with Parkinson's disease complained of disturbing sleep problems, significantly more than in patients with diabetes mellitus (45%), or in aged controls (33%) [1]. There was no difference between groups regarding difficulty falling asleep but Parkinson's disease patients were twice as likely to report frequent (39%) or early morning (24%) awakenings than the other groups. Furthermore, when present, these problems were described as more distressing. The proportion of Parkinson's disease patients affected by "broken sleep" rises to 76% in hospital samples [2].

Repeated sleep-related violence and nocturnal injuries are reported by 15% of patients with Parkinson's disease [3]. REM sleep behavior disorder (RBD), usually reflecting violent or unpleasant dream enactment, is increasingly recognized and affects between 30% and 60% of patients [4,5]. In RBD, there is a striking and unexplained male predominance [6,7] both in Parkinson's disease populations and those who exhibit RBD without clinical parkinsonism (idiopathic or cryptogenic RBD). The latter are at significant risk of developing either Parkinson's disease or a similar neurodegenerative disorder in time [8,9].

Case-controlled epidemiological studies performed in various countries addressing excessive daytime sleepiness (EDS) have consistently found higher levels of somnolence in Parkinson's disease populations compared to age- and sex-matched controls [10–12]. The prevalence of significant EDS is probably around 30% although the figure varies between 16%

and 74% in the published studies. It is even possible that a symptom of EDS may be a harbinger of Parkinson's disease as sleepy adults in a large Asian longitudinal study were 3.3 times more likely than non-sleepy adults to develop Parkinson's disease later in later life [13]. Very severe sleepiness such that patients fall asleep without recognizing the prior imperative to sleep may affect a proportion of patients (1–4%) [14,15]. Such so-called "sleep attacks" have led to major concerns regarding safe driving, particularly in generally less physically disabled younger patient groups.

## Signs and symptoms

### Insomnia

A relative inability to fall and stay asleep appears a natural and inevitable consequence of normal aging. However, in patients with Parkinson's disease, there are frequently additional factors which significantly worsen sleep. In general, there is a correlation between the degree of insomnia and the severity of motor symptoms although it is unclear how much dopamine deficiency per se contributes to the problem. In addition, patients whose disease is advanced tend to be taking increased amounts of Parkinson's disease medication which may confound the picture and contribute to insomnia. A systematic and directed interview is probably the most effective method of assessing insomnia as sleep monitoring rarely reveals specific causes.

Particularly in patients with moderate to severe Parkinson's disease, special attention should be directed to disruptive nocturnal sensory and motor symptoms. Discomfort during the night is particularly common in patients with Parkinson's disease and can have many causes. Symptoms of restless legs may affect 12–21% patients [16,17] although occasionally the combination of leg pain and additional akathisia in Parkinson's disease may mimic true restless legs syndrome. Painful dystonia is also well described, particularly classical "early morning dystonia." Occurring during the latter part of the night, usually after a normal awakening, this typically presents as long-lasting, postural contractions of the toes in flexion or extension, sometimes with internal rotation of the ankle. The dystonic postures and associated discomfort make mobilization difficult and may cause anxiety, inhibiting any attempts to return to sleep. Dystonia affecting other body parts such as the neck and back muscles may also occur only at night, presumably when cerebral dopamine levels are lower.

Nocturnal bradykinesia may also significantly disrupt sleep in some patients with Parkinson's disease and should be addressed. An inability to turn in bed, adjust the pillows, or leave to bed to pass water, for example,

may produce prolonged arousals. The act of voiding urine may take many minutes and may need to be repeated through the night, especially if incomplete or if there is associated confusion. Whether bladder instability contributes to nocturia in patients with Parkinson's disease or whether the desire to pass water occurs only after sleep is fragmented for other reasons remains uncertain. In any event, patients with Parkinson's disease have, on average, twice as many nocturnal awakenings as controls [11] with most reporting between two and five prolonged arousals, lasting 30–40% of the nocturnal period [18–19].

The issue of mood disorder in Parkinson's disease is complex but is likely to impact on sleep quality as an independent factor in some cases. In particular, anxiety may increase nocturnal arousals and depression may disrupt sleep or its timing. In general, poor sleep quality in Parkinson's disease appears to correlate with depression and anxiety scores [20]. Anxiety is also likely to be enhanced by nocturnal hypokinesia.

The role of dopaminergic therapy in causing insomnia should also be considered. Agonists taken at bedtime may effectively act as stimulants and delay sleep onset [21]. The consequences of using supraoptimal doses of dopamine agonists and levodopa day and night should also be addressed in certain patients. Although often in denial, such patients often stay awake and are hyperactive at night, using computers, gambling, or engaging in other compulsive activities. This condition is now commonly identified as the dopamine dysregulation syndrome and affects up to 11% patients with Parkinson's disease [22].

Many patients with Parkinson's disease have great difficulty in waking at a conventional hour, with early rising a particular problem. Whether there is an independent circadian disorder typical for Parkinson's disease, perhaps mimicking advanced sleep phase syndrome, has not been convincingly demonstrated although clock dysfunction in advanced or complex patients seems possible from a theoretical perspective and also from preliminary observations using actigraphy [23].

### **Excessive daytime sleepiness**

Excessive daytime sleepiness (EDS) in Parkinson's disease can be reported by patients or only noticed by the care giver as a significant symptom. In fact, it seems likely that Parkinson's disease patients are particularly poor at recognizing their levels of sleepiness and will frequently even deny sleep episodes captured during objective investigations such as the Multiple Sleep Latency Test [24]. Napping after lunch is frequent in patients with Parkinson's disease and is often perceived as beneficial. In severe cases, the levels of sleepiness can resemble those seen in narcolepsy with sudden naps during activities such as eating a meal, walking, attending work, and, of particular concern, while driving a car.

Sleep attacks can sometimes be confused with fainting caused by orthostatic or postprandial hypotension, symptoms associated with the dysautonomia seen in Parkinson's disease.

The Epworth sleepiness score (ESS) has been assessed specifically in Parkinson's disease [25] and scores above 10, as in other populations, usually suggest a significant problem. However, the ESS is poorly predictive of sleep attacks [14], perhaps due to the potential discordance between subjective and objective sleepiness witnessed in many patients with Parkinson's disease. Some authors have added specific questions to the ESS for Parkinson's disease, addressing the ability to fall asleep when driving, eating, working or performing regular housework activities [14], that might better predict the risk of driving-related accidents.

Given the availability of effective treatment options, it is important to enquire about severe snoring and symptoms compatible with obstructive sleep apnea (OSA) in Parkinson's disease. Since patients with Parkinson's disease tend to be thinner than control groups, the possibility of significant OSA may not be considered.

### **Nocturnal disturbances**

Excessive motor activity during sleep in Parkinson's disease may range from repetitive jerks of the lower limbs reflecting periodic limb movements to less stereotyped and more vigorous activity involving any body part in RBD. Movements in RBD tend to be brief or explosive, often incorporating the upper limbs in defensive maneuvers. Punching, catching invisible objects, and slapping are typical activities, usually with the eyes closed. Purposeful use of nearby objects is exceptional and any violence or injury caused by the disturbance occurs incidentally. The lower limbs tend to be less involved although kicking and bicycling are frequently witnessed. Standing up and walking are very rare during RBD-related movements [7], although some patients with RBD also exhibit associated sleepwalking behaviors arising from non-REM sleep [5]. Vocalization is common and may precede motor activity in the limbs. Groaning, swearing, and crying are typical although laughing and conversational speech are increasingly recognized. Intriguingly, motor activity and speech during RBD is often more fluid than appears possible during waking hours in generally hypokinetic individuals [5]. Subjects can usually be woken relatively easily from an RBD event. Following arousal, congruent dream activity is generally recalled, particularly in typically aggressive episodes. Although injury to the spouse may result, the violent dream often centers on protecting a loved one from animal or human aggressors.

In the presence of significant cognitive impairment, it is frequent for patients with Parkinson's disease, especially those with associated dementia, to display prolonged confusional episodes arising from sleep, sometimes



with associated hallucinatory and delusional intrusions. These events may resemble a form of sleepwalking (i.e. a non-REM sleep parasomnia or "dis-order of arousal") although probably have a different etiology.

## Diagnostic procedures

A directed interview with knowledge of the spectrum of potential sleep-wake problems seen in Parkinson's disease and the relative role of motor, cognitive, and therapeutic factors is the key to successful diagnosis and treatments (table 9.1). Two specific scales, the PD Sleep Scale and the SCOPA-sleep can be helpful for research purposes addressing sleep quality [26,27] but are no substitute for a detailed clinical history. The timing of drug doses can be relevant especially in assessing insomnia, particularly if nocturnal symptoms might reflect dopaminergic underactivity. If restless legs syndrome or periodic limb movement disorder are thought likely contributors, as in other patient groups, it is worthwhile checking ferritin levels for iron deficiency.

If EDS has been recognized, reducing any sedative drugs including opiate painkillers, long-acting benzodiazepines, and sedative antidepressants should be first considered. Recent changes in dopaminergic therapy,

**Table 9.1** Some relevant probes to assess sleep problems in Parkinson's disease

- 
- How long does it take for you to fall asleep after switching off the lights in the evening? (>30 min implies significant sleep-onset insomnia)
  - Do you wake early and find it difficult to return to sleep?
  - Do you have frequent awakenings at night?
  - Are you confused or "not yourself" during these awakenings?
  - Does it take a long time for you to pass urine at night?
  - How often do you need to urinate at night?
  - Can you resume sleep easily after being awake during the night?
  - How long do you sleep at night?
  - Do you experience foot dystonia (curled-up toes) in the early morning?
  - Do you have pain in some parts of your body during the night?
  - Do you experience restlessness in the legs?
  - Are you a snorer? Has your partner witnessed long gaps in your breathing?
  - Are you talking, shouting, or swearing while asleep?
  - Do you have nightmares (e.g. being attacked, defending your family against aggressors)?
  - Has your partner observed you moving, kicking, punching while asleep?
  - Do you have hallucinations at night (seeing somebody or an animal in the bedroom)?
  - Do you fall asleep when inactive during the day?
  - Are you driving a car?
  - Do you struggle to stay awake while driving?
  - Do you experience partial hallucinations during the daytime (the feeling that there is somebody behind you, or that an animal or a person passes by you)?
-

particularly agonists, may also coincide with striking somnolence. Some younger patients appear to exhibit idiosyncratic reactions to agonists such that they suddenly develop EDS at narcoleptic levels [28]. Changing or discontinuing agonist therapies may help in this situation.

The precise roles of nocturnal sleep monitoring in Parkinson's disease and subsequent daytime investigations such as a Multiple Sleep Latency Test are uncertain. Even if previously unexpected severe OSA or PLMs are revealed, their relevance to the overall sleep-wake disturbance is often unclear. However, the full extent of the sleep-wake dysregulation across a 24-hour period may be clearly demonstrated by investigations, and the concept of "secondary" narcolepsy has arisen in severely affected Parkinson's disease patients. Although the sleep-wake profile and investigation results may mimic those of idiopathic narcolepsy, in the absence of cataplexy, the underlying mechanisms are probably different.

If prominent jerks or violent behaviors, suggestive of PLMs or RBD, respectively, are reported, a first step is to check the drug history. The majority of antidepressants, including serotonin reuptake inhibitors and mirtazepine, in particular, can exacerbate general motor restlessness, PLMs and RBD. Even if RBD appears extremely likely from the history, some authorities advocate nocturnal sleep and video monitoring to address the possibility of prolonged apneic events in REM sleep triggering motor restlessness.

It should be mentioned that there may be particular problems with interpreting polysomnograph data, particularly in patients with advanced Parkinson's disease and especially if automated systems are used. Dissociated sleep states, including RBD, are frequently seen and phenomena such as continuous alpha background rhythm, nonspecific sleep artefacts, continuous eye movements during sleep combine to make accurate or reliable sleep staging very difficult (table 9.2).

**Table 9.2** Abnormal findings on polysomnography and MSLT in Parkinson's disease

	Abnormalities	Indicates
EEG	Slow (< 8 Hz) alpha rhythm during relaxed wakefulness	Possible cortical degeneration. Frequently associated with RBD
	Continuous alpha rhythm during all sleep stages	Unknown. Complicates the scoring process (not to be confused with complete insomnia)
Eye movements	Can be present during stage 2	Sleep dissociation. Complicates the scoring process. No associated clinical problem
	Square-wave jerks during wakefulness and REM sleep	Raises possibility of progressive supranuclear palsy as diagnosis

**Table 9.2** (Continued)

	Abnormalities	Indicates
Chin muscle tone	Enhanced tonic activity during REM sleep Increased twitching during REM sleep	REM sleep without atonia, preceding or associated with RBD Possible vocalization
Leg EMG	Frequent, periodic 0.5-5 s bursts  4-6 Hz bursts  2 Hz left/right alternating bursts Long-lasting, prominent activity. Complex vigorous movements during REM	Periodic leg movement syndrome, possibly associated with restless legs syndrome  Parkinsonian tremor persists in sleep (can be seen on the chin too) Alternative leg movement activity Dystonia of leg muscles. RBD
Respiratory sensors	Apneas Stridor (inspiratory, harsh sound)	Sleep apnea syndrome Multiple system atrophy more likely, reconsider diagnosis. Treat stridor (see chapter 10)
MSLT	Mean latency lower than 8 min  Two or more sleep-onset REM periods (usually without atonia)	Objective sleepiness demonstrated Criteria for secondary narcolepsy met

## Management

### Insomnia

Perhaps appropriately, there are no protocols or formal guidelines for treating insomnia in relation to Parkinson's disease and a flexible experience-based approach is much more useful than one hoping to rely on population-based trial data (table 9.3). Simple measures to improve overnight comfort may often be overlooked. Examples include the use of sheets and bedclothes that slip easily and pyjamas without buttons. Similarly, having medication, water and other items such as a phone within easy reach of the bed may make a useful difference. Some parkinsonian patients develop rigid patterns of behavior with respect to sleep-wake habits and drug taking. For example, some will set alarm clocks to take their first Parkinson's disease drug prescribed at a precise early morning time, and then have difficulty in resuming sleep. Others might retire to bed at a fixed hour but be unable to fall asleep, generating further anxiety. In such cases, advice to be more flexible with sleep and drug timings may be beneficial.

**Table 9.3** Management suggestions for sleep problems in patients with Parkinson's disease

Problem	Suggestive of	Proposed management
<i>Frequent (&gt;2) micturitions at night</i>		
Normal volumes	Sleep apnea syndrome?	Check for sleep apnea and treat appropriately
Small volumes, poor stream	Prostatism	Refer to urologist
Small volumes, good stream	Parkinsonism-associated polyuria	Try intranasal desmopressin in the evening. Have a bottle for collecting urine in the bedside table or an overnight sheath for males
<i>Difficulty to initiate sleep</i>		
Early in the evening	Lights off too early (patient going to bed fatigued but not necessarily sleepy)	Switch off lights later
	Anxiety, or behavioral insomnia	Sleep hygiene. Treat anxiety. Evening melatonin. Zolpidem, zopiclone
With restlessness	Restless legs syndrome	Check for low ferritin. Remove antidepressant drugs. If the diagnosis is uncertain, consider polysomnography with legs monitoring. Try gabapentin. Try an opiate such as Tramadol 100 mg if not confused
Late in the night	Altered circadian cycle?	Sleep hygiene. Decrease levodopa/dopamine agonists in the evening. Melatonin at end-afternoon
Late in night, hyperactive, hypomanic	Assess for dopamine dysregulation syndrome	Remove dopamine agonists. Keep on levodopa monotherapy. Close neuro/psychological follow-up
<i>Difficulty to resume sleep</i>		
With cramps, muscle pain, slowness	Nocturnal akinesia	Try immediate-release levodopa with a glass of water during awakening. Try long-acting dopamine agonists
With restlessness	Restless legs syndrome	Check for low ferritin. Remove antidepressant drugs. Try gabapentin. Try Tramadol 100 mg if not confused
With anxiety	Anxiety disorder	Try evening antidepressant such as amitriptyline 10 mg
With low mood	Depressive disorder	Treat the depression
<i>Nightmares, agitation</i>		
Confused at night when awake	Presence of hallucinations?	Remove/reduce the evening dose of dopamine agonist and the antidepressant. Check for sleep apnea; try antipsychotic such as quetiapine/clozapine

**Table 9.3** (Continued)

Problem	Suggestive of	Proposed management
Kicks, shouts, slaps	REM sleep behavior disorders	Secure the bed environment. Reduce antidepressant. Assess likelihood of sleep apnea and consider performing video PSG before treating. Try clonazepam 0.5-2 mg in the evening. Try melatonin 3-9 mg in the evening
<i>Daytime sleepiness</i>		
Falls asleep unexpectedly	Sleep attacks?	Check for possible inducing drugs (dopamine agonist), and remove/change. Warning regarding driving.
Excessive and troublesome EDS		Explore levels of sleepiness, consider Epworth sleepiness score. Consider polysomnography and MSLT. Ask about associated hallucinations. Treat sleep apnea if severe. Decrease/stop the dopamine agonist during daytime, and other sedative drugs. Try modafinil or methylphenidate. Consider sodium oxybate in severe cases

Improving the continuity of sleep by manipulating dopaminergic therapy can often be successful, especially in the presence of likely dystonias or hypokinetic symptoms disturbing nocturnal sleep. Long-acting agonists such as the rotigotine patch before bed may be useful but the evidence for superior efficacy over oral agents such as pramipexole is lacking, at least in nonselected groups of advanced patients [29]. Simple use of levodopa (200 mg) taken mid-evening has been assessed and found to reduce excessive nocturnal movement and improve subjective sleep quality [30]. However, randomized comparisons with sustained-release levodopa preparations are lacking. Immediate-release levodopa may also be used with success for prolonged nocturnal arousals. Alternatively, if there are symptoms suggesting nocturnal overarousal or intrusive dreams, for example, reducing dopaminergic treatments late in the day may help the situation.

Even if it is not a primary sleep "toxin," nocturia is a frequent symptom of concern that may lead to practical difficulties with micturition, especially if confusion is present. One simple strategy is to use a bottle or bedpan or even a convene sheath, in males, averting the need to leave the bed. The use of desmopressin spray to suppress urinary output is probably safe and may be worthy of consideration in some patients with Parkinson's disease.

Hypnotic drugs and neuroleptics are sometimes used in attempts to improve sleep continuity in Parkinson's disease although published evidence to guide drug choice is very limited. Single, small, unblinded trials of zolpidem, clozapine for nocturnal akathisia, and quetiapine have shown a benefit on sleep in patients with Parkinson's disease. Even in the absence of RBD, clonazepam (0.5–2 mg) can be used empirically, especially if the risk of sleep apnea is low. In clinical practice, low doses of sedative antidepressants such as amitriptyline (5–10 mg) are frequently used, with variable and often unpredictable success rates. Many antidepressants, particularly tricyclics, however, can worsen sleep quality even if sleep time is prolonged.

Patients with varying degrees of cognitive impairment, nocturnal hallucinations, and confusional arousals present particular problems for drug therapy. If adjustment or reductions of existing therapy have not helped, additional use of antipsychotic agents such as quetiapine (12.5–100 mg) or clozapine (12.5–50 mg) is favored by some, even though the latter requires regular monitoring for the rare adverse event of agranulocytosis. Increasing anecdotal evidence suggests that cholinesterase inhibitors such as rivastigmine, perhaps delivered via the transdermal patch (9.5 mg), are very useful in this difficult group and may help to restore sleep continuity. However, care should be taken with this approach as some patients develop nightmares or even hallucinations, presumably as a result of increased REM sleep density induced by cholinergic drugs.

The role of subthalamic (STN) stimulation in improving insomnia symptoms has received recent attention. Certainly if hypokinesia or dys-tonias are prominent symptoms at night, it appears to improve sleep efficiency substantially [31]. The resulting reductions in dopaminergic therapy that usually follow STN stimulation may also improve sleep quality in some individuals.

### **Restless legs syndrome**

In the absence of iron deficiency, the treatment of nocturnal restless legs syndrome in Parkinson's disease may be complex and there is little published guidance. Anticonvulsants such as gabapentin and pregabalin may improve the sensory discomfort and, if there are no significant neuropsychiatric problems, opiates may be used successfully [17]. Although increasing nocturnal dopamine stimulation would seem logical in this situation, some hold the theory that nocturnal restless legs syndrome in Parkinson's disease reflects the phenomenon of "augmentation" secondary to excessive dopamine daytime stimulation. This might be supported by the development, in some, of restless legs syndrome several years after the motor symptoms of parkinsonism. If this hypothesis were true, paradoxical reduction of daytime dopaminergic drugs would be a more appropriate approach.

### **REM sleep behavior disorder**

In significant RBD, patients should secure their bed environment and partner, perhaps by placing a pillow between them, using twin beds, or having the mattress directly on the floor. Removing nearby objects such as tables and lamps is also sensible. If existing drug treatments such as antidepressants are thought contributory, they should be stopped if possible. Furthermore, if investigations confirm significant sleep-related breathing disorders, the use of a nasal positive airway pressure device can sometimes reduce the abnormal nocturnal behaviors and the need for further drug treatment.

If pharmacotherapy is thought appropriate, there is a lack of randomized, double-blind, placebo-controlled studies but clonazepam is widely regarded as the first-line treatment (0.5–2 mg), especially if sleep apnea has been excluded or treated. Efficacy and tolerance are usually good [32]. There is debate whether other hypnotic agents are as effective as clonazepam in RBD or whether clonazepam has a particular pharmacological profile of benefit.

Increasing evidence suggests that melatonin is also effective and well tolerated in RBD, probably in a dose range 2–9 mg. Of interest, the drug appears to partially restore normal muscle atonia during REM sleep in patients with Parkinson's disease [33,34], in contrast to clonazepam which simply attenuates the phenomenon, perhaps reducing violent jerks to minor twitches. Dopaminergic agents, in general, do not alter RBD in symptomatic patients [6,35].

### **Excessive daytime sleepiness**

If EDS is a symptom of concern to patients or their carers, initial efforts should be directed to reducing potentially sedative drugs including dopamine agonists, sedative antidepressants, opioids and clonazepam, if possible. The utility of planned daytime naps has not been assessed systematically but appears to benefit some.

The use of wake-promoting therapy is often appropriate if simple measures have failed to help. Perhaps due to the complexities and variable causes of EDS in Parkinson's disease, the published evidence regarding the success of drugs such as modafinil is mixed [36]. However, modafinil is generally safe and an empirical trial of therapy is often warranted. An overall positive response in approximately 30% of patients might be expected. More traditional psycho-stimulants such as methylphenidate have been used less frequently although they might be especially useful if atypical depression, anhedonia or apathy are prominent additional symptoms.

A new approach to EDS in Parkinson's disease mirrors that used in narcolepsy. In particular, there is early uncontrolled trial evidence that

nocturnal sodium oxybate may help to consolidate sleep in Parkinson's disease and subsequently improve daytime wakefulness, as in narcoleptics. Significant reductions in Epworth scores from 16 to 9 were reported [37].

## Conclusion

Hopefully it is clear that virtually every aspect of the sleep-wake cycle can be disrupted in Parkinson's disease, especially in advanced cases. Interactions between drug therapies and the underlying disease process can interfere with sleep and daytime wakefulness such that manipulations in pharmacotherapy may improve one aspect but worsen another. In view of the potential complexity of the sleep problems in Parkinson's disease, perhaps contrary to expectations, treatments can frequently benefit subjects and improve quality of life, especially for carers. It should be emphasized that any management pathway, particularly involving drugs, should be flexible and individualized. With increasing awareness of sleep-wake issues in Parkinson's disease, it is difficult to know when a movement disorder specialist should involve the expertise of a specific sleep clinic. However, a multidisciplinary approach is probably the best solution if resources allow.

### Key points

- Virtually every sleep-related problem across the 24-hour period can occur in Parkinson's disease, particularly in advanced cases with neuropsychiatric symptoms.
- The direct role of dopamine deficiency in causing daytime sleepiness or overnight sleep disruption is often uncertain and other neurochemical systems are probably at least as important.
- Some patients develop paradoxical severe daytime sleepiness with dopamine replacement therapy, particularly after starting agonists, perhaps as an idiosyncratic reaction.
- A major cause of overnight sleep disruption is motor disability.
- Violent dream enactment (REM sleep behavior disorder) is particularly common in patients with Parkinson's disease and often precedes motor symptoms.
- Formal sleep investigations tend not to be particularly useful in the assessment of insomnia or hypersomnolence other than confirming poor-quality sleep and narcoleptic levels of daytime sleepiness.
- Treatment of sleep-related problems in Parkinson's disease should be individualized to the specific symptoms elicited from a detailed 24-hour history.
- Manipulating dopaminergic therapy can sometimes be useful, as can providing hypnotic agents to improve overnight sleep and/or wake-promoting drugs during the day such as modafinil.



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## CHAPTER 10

# Sleep disorders in Parkinson's-plus syndromes

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### Introduction

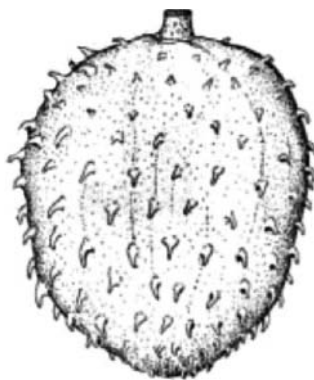
There are several disorders which associate atypical parkinsonism (e.g. symmetrical, early falls or poor levodopa responsiveness) with other neurological signs, such as cerebellar, oculomotor, or pyramidal dysfunction. The most important of these so-called “Parkinson-plus syndromes” are multiple system atrophy (MSA) and progressive supranuclear palsy (PSP, Steel-Richardson-Olszewski syndrome).

Multiple system atrophy is the most frequent Parkinson-plus syndrome and belongs to the synucleinopathies. Sleep disturbances are very common in MSA, and include insomnia, abnormal movements during sleep, and EDS. In MSA, sleep-disordered breathing is a particularly important element, as it may take the form of nocturnal stridor. Nocturnal stridor may result in life-threatening episodes of respiratory failure with sudden death during sleep, and should therefore be treated promptly.

Progressive supranuclear palsy belongs to the tauopathies, and may show a somewhat different spectrum of sleep disturbances. While insomnia and EDS are common, REM sleep behavior disorder (RBD) is much less common compared to the synucleopathies.

Finally, there is a rare but interesting toxic tauopathy, “Guadeloupean parkinsonism,” caused by ingestion of soursop, a tropical fruit (figure 10.1). Patients have a PSP-like syndrome, often with insomnia. Furthermore, RBD is ubiquitous, especially on polysomnography.

Sleep disorders in Parkinson-plus syndromes often have a severe impact on the quality of life, and are therefore important to identify. Conversely, the presence of specific sleep disorders can sometimes help



**Figure 10.1** Soursop, a tropical fruit containing anonacin, a mitochondrial poison. Its consumption is associated with the atypical parkinsonism observed in Guadeloupe, in which almost all patients have REM sleep behavior disorder.

to identify the exact movement disorder diagnosis. For example, nocturnal stridor strongly suggests the presence of MSA, while prominent RBD makes a tauopathy less likely.

## Clinical epidemiology

Compared to Parkinson's disease, sleep disorders are even more frequent in MSA. As many as 70% of patients with MSA have sleep complaints, including sleep fragmentation (53%), early waking (33%), and insomnia (20%) [1]. Excessive daytime sleepiness is present in about 50% of such patients [2]. Although the prevalence of restless legs syndrome is only a little higher than the general population, periodic limb movements are recorded in almost all MSA patients [3]. Nocturnal hallucinations seem to be much less common in MSA compared to Parkinson's disease. The most important nocturnal sleep disorders in MSA are RBD and sleep-disordered breathing. REM sleep behavior disorder affects 90–100% of patients [3,4], and may precede the onset of MSA by years [5]. Interestingly, RBD has been reported to disappear with evolution of the disease [6]. Sleep apnea is estimated to affect up to 37% of patients [3,4]. Prevalence estimates of nocturnal stridor, clinically the most important form of sleep-disordered breathing, differ widely, ranging from 13% to 69% [2,7,8].

Large epidemiological studies on sleep in PSP are not available, but a case series with PSG showed severe insomnia in all subjects, with total sleep time between 2 and 6 hours and an average time awake per night of more than 4 hours [9]. Clinically, RBD is present in less than 15% of patients with PSP. REM sleep without atonia is detected on PSG a little

more often, in about 30% of patients. The prevalence and severity of EDS is comparable to that found in Parkinson's disease [10].

## Signs and symptoms

Many of the sleep problems in Parkinson-plus syndromes are manifestly similar to Parkinson's disease (see chapter 9). The most salient are discussed here, with highlighting of disease-specific symptoms.

In general, the movement symptoms of Parkinson-plus syndromes are poorly levodopa responsive. Therefore, insomnia is often caused by nocturnal motor symptoms which can be hard to treat. Rigidity and "off"-dystonia can further induce pain, contributing to sleep fragmentation. Finally, autonomic dysregulation can result in urinary dysfunction, with nocturia and nocturnal incontinence.

Daytime sleepiness can be a prominent feature, especially in MSA. Sometimes, sleepiness is exaggerated by meals. Autonomic dysregulation may sometimes lead to postprandial hypotension, and this must be distinguished from sleepiness.

In MSA, RBD is very prevalent [11]. Beside resulting in sleep fragmentation, RBD can sometimes be harmful to the patient or partner [12]. It therefore is important to diagnose RBD, and start appropriate treatment (see table 10.1). Interestingly, the movements of RBD are much more vigorous and rapid than expressed during the day, a phenomenon that has also been reported in Parkinson's disease [13,14]. In Guadeloupean parkinsonism, RBD is reported to be present in virtually every patient.

Besides "common" obstructive sleep apnea, central alveolar hypoventilation is relatively common in MSA. It is probably caused by degeneration of pontomedullary respiratory centers. Most importantly, MSA is associated with nocturnal stridor, caused by a combination of vocal cord paralysis and excessive adductor activation during inspiration (table 10.2). Nocturnal stridor can occur in all clinical stages of the disease, and even as the first symptom [15]. It is characterized as a harsh, high-pitched, inspiratory crowing sound. It can be very loud, and often disturbs the sleep of the bed partner. Although very distinct from normal heavy snoring, snoring and stridor can co-occur and even "mix," making the diagnosis less easy.

## Diagnostic procedures

The most important diagnostic tool remains a thorough clinical interview. In addition, sleep recordings, especially nocturnal video-polysomnography, play a central role in the diagnostic process.

**Table 10.1** Diagnosis and management of REM sleep behavior disorder in patients with Parkinson-plus syndromes*Search for RBD in all patients*

- Ask for nocturnal behaviors such as laughing, shouting, swearing, kicking, fighting, etc.
- Differentiate stereotyped, periodic leg movements from the variable behaviors associated with dreaming
- Ask about “bad dreams,” and relation between dreams and behaviors
- Evaluate severity: frequency, violence associated with dream enactment

*Confirm RBD on videopolysomnography*

- Look for REM sleep without atonia, and/or
- Observe motor behaviors during REM sleep
- Search for sleep-disordered breathing. It is important to distinguish RBD from apnea arousals, especially in MSA

*Treatment*

- Mild RBD (infrequent, only vocalizations with light movements): no treatment necessary, re-evaluate when symptoms get worse
- Severe RBD (violent, resulting in frequent sleep disruption):
  - Secure sleeping environment: pillow between patient and co-sleeper, separate beds or bedrooms, put the mattress on the floor, remove objects around the bed
  - Reduce or withdraw possible RBD-inducing drugs, especially antidepressants
  - Start clonazepam, 0.5–2 mg at night, when there is no severe sleep apnea
  - If ineffective, or when there is severe sleep apnea: try melatonin, 3–12 mg at night

**Table 10.2** Diagnosis and management of stridor*Search for possible stridor*

- Ask co-sleeper whether the patient makes “a strange noise” while sleeping
- Mimic the noise of stridor to help the co-sleeper recognize it
- Mimic the noise of snoring to help the co-sleeper differentiate it from stridor
- Ask for stridor during wakefulness

*Confirmation*

- Every patient with suspected stridor should have a video-PSG as soon as practically possible
- Video-PSG: search for inspiratory crowing, harsh, high-pitched sound during sleep
- Laryngoscopy: evaluate vocal cord motility

*Management*

- The presence of stridor is a “red flag” for MSA: revise diagnosis if necessary
- Start nocturnal continuous positive airway pressure therapy
- When stridor is present night and day, or if there are prominent swallowing difficulties: consider tracheostomy, taking into account the patient’s quality of life and life expectancy

A complaint of insomnia can be further specified using a sleep diary for two consecutive weeks. This diary can also be used to record daytime sleep episodes and napping habits.

When EDS is a prominent complaint, it may be useful to confirm using an MSLT (see chapter 3). This makes it also easier to distinguish sleepiness

from fatigue, which is very prevalent in patients with Parkinson-plus syndromes [10].

The diagnosis of RBD requires a history of recurrent dream enactment behavior in combination with polysomnographic confirmation. For the latter, the presence of REM sleep without atonia is sufficient. However, the recording of complex motor behavior during REM sleep on video makes the diagnosis of RBD certain [16]. In Parkinson-plus syndromes, polysomnography is especially important to distinguish RBD from complex movements that may be associated with sleep-related breathing disorders [17].

The diagnosis of sleep-disordered breathing requires polysomnographic confirmation, including audio recordings. This allows the differentiating of central breathing disorders from obstructive apnea. Audio monitoring is essential to identify the characteristic sound of nocturnal stridor. When nocturnal stridor is suspected, the patient should be referred for fiberoptic laryngoscopy to detect partial or complete abduction restriction of the vocal cords during inspiration, sometimes associated with low amplitude dystonic-like movements [18].

## Management

### Insomnia

In general, the therapeutic approach to sleep disturbances does not differ between Parkinson's disease and Parkinson-plus syndromes (see also chapter 9). The treatment of insomnia consists of two strategies: specifically treating sleep-fragmenting symptoms and/or specifically improving sleep continuity, for example with hypnotics.

Nocturia is an important cause of sleep fragmentation. Behavioral strategies are always important, such as restriction of fluid intake in the evening, or the use of a condom catheter in some cases. Anticholinergic bladder tocolytics may be useful (after exploration and treatment of possible prostatism). Furthermore, desmopressine (0.2–0.4 mg in the evening) often has good effect.

If there is any sign of dopamine responsiveness, one could attempt to treat nocturnal rigidity and hypokinesia with administration of long-acting dopaminergics in the evening, or immediate-release levodopa during awakenings at night. Because dopamine responsiveness is often poor in Parkinson-plus syndromes, non-pharmacological "treatment" of these symptoms is all the more important, ranging from silk pyjamas to physical therapy interventions, for example to teach strategies to turn around more easily in bed. Nocturnal ("off") dystonia resulting in pain can sometimes be treated with local injections of botulinum toxin. Nonspecific pain medication can be helpful in patients with painful

akinesia, rigidity, or dystonia, especially when there is insufficient response to dopaminergics.

Sleep continuity can also be improved by hypnotics, or small doses of sedative antidepressants (see also chapter 5). Both benzodiazepines or “Z” drugs have been reported to be useful. Sedative antidepressants may include amitriptyline (5–10 mg), mirtazipine (15–30 mg), or trazodone (100–200 mg). However, it is important to check for possible exacerbation of restless legs syndrome or RBD. Antidepressants sometime have the beneficial anticholinergic side effect of reducing nocturia. In patients with hallucinations or delusions, low doses of clozapine (25 mg) can be helpful, provide there is a regular check of the white blood cell count.

Restless legs syndrome in Parkinson-plus syndrome may be very hard to treat. When there are low ferritin levels, iron supplementation should always be attempted. Sometimes dopaminergics may have an effect. If not, opiates or gabapentine may still be useful [19].

### **REM sleep behavior disorder**

The role of medication that can induce or exacerbate RBD should always be recognized, and offending drugs reduced or withdrawn if possible. Most important in this respect are the antidepressants, including serotonin reuptake inhibitors. The bed environment should be secured, to prevent injury of the patient or the bed partner [20]. Clonazepam is the treatment of first choice (see table 10.1). If not effective, melatonin may sometimes restore muscle atonia during REM sleep and decrease severity of RBD [21].

### **Excessive daytime sleepiness**

Always check for the presence of sedative drugs, for example long-acting benzodiazepines or opiates. Recent introduction or change of dopamine agonists should also raise suspicion when EDS is developing. Unfortunately, offending drugs can often not be missed in Parkinson-plus syndromes. Sleep-related breathing disorders are common and should actively be sought and treated. Stimulant medications have not been formally evaluated, but may be worth trying (chapter 6).

### **Nocturnal hallucinations, psychosis, and confusion**

Unfortunately, when used during the day or in the evening, dopaminergic medications may induce entirely new sleep problems. Vivid dreams, nightmares, and night terrors occur in up to 30% of patients with parkinsonism who are taking levodopa, especially those with dementia. In patients with Parkinson-plus syndromes, a reduction of afternoon or evening levodopa doses is usually sufficient to control this phenomenon. Low evening doses of clozapine (12.5–25 mg) can sometimes be helpful.



### Sleep-disordered breathing

In patients with obstructive sleep apnea, continuous positive airway pressure (CPAP) offers the best chance of success and can be used effectively by most patients with parkinsonism until the advanced stages of the disease are reached.

In patients with MSA, the treatment of stridor must be started as soon as possible, since stridor can induce life-threatening episodes of respiratory failure and sudden death during sleep (see table 10.2). Continuous positive airway pressure is an effective noninvasive treatment to eliminate stridor [18,22,23]. While untreated stridor is associated with short survival [24], stridor patients treated with CPAP have the same survival as patients without stridor. Experience with botulinum toxin is limited [25]. This therapy is invasive and may increase the risk of bronchial aspiration and may aggravate dysphonia and dysphagia. When CPAP is not tolerated, or stridor is also present in wakefulness, tracheostomy should be considered. Central alveolar hypoventilation during sleep may sometimes respond to CPAP treatment. However, other ventilatory techniques, especially adaptive servo-ventilation (ASV) [26] may be necessary.

#### Key points

- Sleep disturbances in Parkinson-plus syndromes may be prominent, and sometimes have a different pattern compared to Parkinson's disease.
- Poor dopamine responsiveness often complicates treatment of nocturnal sleep disorders.
- Nocturnal stridor in MSA should be actively sought after and treated, as it is associated with a significantly lower life expectancy.

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## CHAPTER 11

# Sleep in other neurodegenerative diseases

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In this chapter, the prevalence and nature of sleep disorders in a variety of neurodegenerative disorders are discussed with particular reference to Alzheimer's disease and dementia with Lewy bodies, Huntington's disease, and the hereditary ataxias.

## Dementias

### Alzheimer's disease

Alzheimer's disease is characterized by progressive cognitive impairment with a variable combination of memory loss, aphasia, apraxia, agnosia, and psychiatric symptoms. Pathological studies demonstrate tau deposits, amyloid plaques, and neurofibrillary tangles in the hippocampus, limbic system, and cortex. Sleep disturbances are undoubtedly common and varied in Alzheimer's disease and may occur at any stage of the disease. Sleep-related problems arise from multiple factors including the degenerative process itself, damaging areas which modulate sleep (e.g. suprachiasmatic nucleus in the hypothalamus, cortex); associated psychiatric disturbances (e.g. depression, agitation); medical issues (e.g. infections, pain); and side effects of medications (e.g. insomnia, EDS). Impaired sleep almost certainly affects quality of life in patients, relatives, and caregivers alike, potentially leading to patient institutionalization. Such disorders include sleep-onset insomnia, sleep fragmentation, early awakening, circadian rhythm disorder, EDS due to frequent napping, nocturnal hallucinations, confusional nocturnal wandering, and sundowning [1]. Surprisingly, no data exist on the prevalence and clinical significance of sleep-disordered breathing, restless legs syndrome, and periodic limb movement disorder in Alzheimer's disease. One small study involving 15 patients with

Alzheimer's disease showed that RBD is uncommon [2], perhaps because brainstem damage is not prominent.

Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine (an N-methyl-D-aspartate antagonist) are used primarily as symptomatic agents at mild and moderate stages of the disease. They may all induce sleep-onset insomnia. Conversely, the frequent use of typical and atypical antipsychotics, usually for agitation or behavioral problems, usually induce hypersomnia.

Treatment of sleep disorders in Alzheimer's disease is challenging and should be individualized. Melatonin and phototherapy can be considered in subjects with circadian dysrhythmia. Nocturnal agitation, hallucinations, confusional awakenings, and nocturnal wandering may improve with atypical antipsychotic agents at bedtime. Use of drugs such as risperidone, quetiapine, and olanzapine, however, may be partly limited by concerns over increased mortality due to stroke [3]. Sleep-disordered breathing can be treated with continuous positive airway pressure. Insomnia, when required, can be usefully treated with trazodone at bedtime or other sedative antidepressants. Modafinil, a central nervous system stimulant, may improve EDS in selected cases.

### **Dementia with Lewy bodies**

Dementia with Lewy bodies (DLB) is clinically characterized by dementia, parkinsonism, recurrent visual hallucinations, and fluctuations in cognition and alertness. Dementia with Lewy bodies is diagnosed if dementia precedes or appears within one year before the onset of physical symptoms of parkinsonism. Although memory function is impaired, there is a different profile of cognitive dysfunction pattern in DLB, compared to Alzheimer's disease, with characteristic deficits of visuospatial ability, attention, and executive function. Neuronal loss, gliosis, neurites, and Lewy bodies are found in the brainstem, limbic system, and neocortex. The combination of brainstem and cortical Lewy bodies is necessary for the pathological diagnosis of DLB [4].

No published data exist on the epidemiology and specific characteristics of sleep disorders in patients with DLB. The author's clinical experience suggests that, as in Alzheimer's disease, sleep-onset insomnia, sleep fragmentation, early awakening, circadian rhythm disorder, EDS due to frequent napping, nocturnal hallucinations, and confusional nocturnal wandering are frequent, particularly in advanced stages of the disease. In contrast, sleep-disordered breathing, restless legs syndrome, and periodic limb movement disorder, although frequent, are no more prevalent than in the general elderly population.

The literature on RBD in DLB is limited, and no published studies have prospectively addressed the prevalence, demographic, clinical, or

video-polysomnographic characteristics of RBD in patients with DLB. We have identified 17 consecutive DLB patients with RBD confirmed by video-polysomnography who were referred to our sleep center (unpublished data). Sixteen patients were male and the mean age of RBD onset was 65 years. In all instances, RBD preceded the onset of cognitive complaints. Unpleasant dream recall was absent in 3 (17.6%) and 10 (58.8%) were unaware of their nocturnal behaviors. Neuropathological examination at autopsy in three patients confirmed the diagnosis of DLB. On the other hand, 12 other patients diagnosed with idiopathic RBD in our center have subsequently developed DLB after several years of close clinical follow-up. Autopsy examination in one of them confirmed the diagnosis of DLB. It has been observed that some idiopathic RBD patients subsequently develop cognitive and motor symptoms either in tandem or separated by just a few months.

In 2005, the diagnostic criteria of DLB considered RBD as a *suggestive* feature of the disease because “it has been demonstrated to be more frequent than in other dementing disorders” [4]. This statement was based on a single retrospective study involving 37 consecutive patients with dementia plus RBD [5]. Thirty-four of these patients (92%) were male. In 35 (96%) RBD symptoms preceded or occurred simultaneously with the cognitive complaints. Of the 37 patients, 23 fulfilled the 1996 consensus criteria for probable DLB (dementia plus at least two of the following: parkinsonism, visual hallucinations, and fluctuations), and all fulfilled criteria for possible DLB (dementia plus one of the following: parkinsonism, visual hallucinations, and fluctuations) [6]. The diagnosis of DLB was confirmed in the three patients that underwent autopsy, supporting the contention that the combination of dementia and RBD most often reflects DLB. This is in agreement with neuropathological studies in patients with ante-mortem diagnosis of DLB plus RBD showing cell loss and Lewy bodies in the brainstem, limbic system, and neocortex [7].

Treatment of sleep-related symptoms in DLB is challenging and controlled evidence is lacking. A similar approach to that in advanced Parkinson’s disease is appropriate and the reader is referred to chapter 9.

## Huntington’s disease

Huntington’s disease is a genetic autosomal dominant neurodegenerative disorder characterized by progressive dementia, chorea, and psychiatric disturbances as a result of expanded CAG repeats in the Huntington gene. Pathological studies demonstrate severe atrophy of the caudate and putamen, and, to a lesser extent, of the cortex [8]. Sleep disorders are undoubtedly common among patients with Huntington’s disease, particularly in advanced stages. Patients and carers usually report poor sleep quality with

sleep fragmentation and frequent awakenings at night. Possibly as a result, EDS is common. In addition, apparent circadian rhythm disorders, typically of the advanced phase type, resulting in early morning awakening are described [9–11]. Interestingly, a transgenic model of Huntington's disease in mice has disrupted circadian rhythms that worsen as the disease progresses, suggesting a progressive impairment of the suprachiasmatic nucleus in the hypothalamus [12].

In a community survey study with 292 patients, sleep problems were reported by 87% and were rated as important by 62%. Sleep problems in rank order were restless limb movements, periodic jerky movements, waking during the night, hypersomnia, and early awakening [9]. In one study involving 25 patients, 64% complained of insomnia, advanced sleep phase occurred in 40%, and hypersomnia in 32% [10].

Overall, polysomnographic studies show reduced sleep efficiency, increased wake time after sleep onset, increased percentage of light sleep, increased REM sleep latency, and reduced percentage of deep sleep and REM sleep [10,13–15]. In Huntington's disease, sleep complaints and polysomnographic abnormalities increase with disease severity and duration [10,13,14]. Polysomnograph studies have shown a low incidence of sleep apnea in patients with Huntington's disease [10,13,15–17] and REM sleep behavior disorder [10]. Multiple sleep latency tests were performed in only one study, showing a reduced sleep latency in 4 of 25 patients (16%) and no REM sleep periods [10].

In a pathological study, a mean reduction of hypocretin cells of 27% was observed in five Huntington's disease brains [18]. In general, Huntington's disease patients do not have a narcoleptic phenotype because cataplexy is absent [10], the multiple sleep latency does not detect sleep onset of REM sleep periods [10], and hypocretin-1 level in the cerebrospinal fluid was found to be normal in 22 living patients [19] and in samples from 10 autopsy subjects [20]. Surviving hypocretinergic neurons in the hypothalamus presumably still provide sufficient hypocretin to prevent the occurrence of hypersomnia and other narcoleptic features.

### **REM sleep behavior disorder in Huntington's disease**

To date, the presence of RBD has only been investigated by clinical history and polysomnography in one study that involved 25 patients. Three (12%) had RBD confirmed by video-polysomnography. Two were aware of their abnormal behaviors at night, but behaviors were considered clinically mild. In an additional patient, video-polysomnography showed RBD but the patient was not aware of displaying dream-enacting behaviors or having unpleasant dreams. The three patients with RBD were two women and one man aged 41, 45, and 65 years, respectively. Huntington's disease was considered mild in one and moderately severe in two [10]. In another

study of 30 patients with Huntington's disease, seven (23%) patients and bed partners reported symptoms suggestive of RBD but polysomnography was not performed [11].

### **Restless legs syndrome in Huntington's disease**

In a series of 25 patients, only one had typical restless legs syndrome. A PLMS index greater than 15 was found in 6 (24%) [10] although in these, the PLMs did not fragmented sleep. In contrast, one study with six patients found a high mean PLMS index of 123 that fragmented sleep architecture [15]. A 55-year-old man developed RLS three years before the onset of the classical symptoms of Huntington's disease and polysomnography demonstrated high indices of periodic leg movements during sleep (index of 58) and wakefulness (index of 79). Restless legs syndrome symptomatology and sleep quality improved dramatically with gabapentin [21]. Restless legs syndrome was described in one family with Huntington's disease. All five family members with restless legs syndrome had Huntington's disease, but some family members with Huntington's disease did not have restless legs syndrome, suggesting an independent occurrence of RLS in this family [22].

## **Hereditary ataxias**

Hereditary ataxias are genetic neurodegenerative disorders with a variable mode of inheritance, including autosomal dominant (e.g. spinocerebellar ataxias), autosomal recessive (e.g. ataxia telangiectasia, Friedreich ataxia), and X-linked (e.g. fragile X tremor ataxia syndrome). Although these diseases predominantly affect the spinocerebellar tracts, cerebellum, and brainstem, other structures in the brain are frequently involved. Clinically, they are characterized by progressive ataxia and a potential plethora of neurological symptoms and signs such as polyneuropathy and parkinsonism [23]. The occurrence and clinical relevance of sleep disorders have received relatively little attention, although several reports have addressed the presence of RBD and restless legs syndrome.

### **REM sleep behavior disorder in hereditary ataxias**

Although generally recognized as an accompaniment to parkinsonian syndromes, RBD also appears highly prevalent in other neurodegenerative conditions, including hereditary ataxias.

Spinocerebellar ataxia type 3 (SCA3 or Machado-Joseph disease) is an autosomal dominant disorder linked to CAG-trinucleotide repeat expansions in the ataxin-3 gene [23]. In a recent study 53 patients reported significantly more sleep-related symptoms than controls, especially regarding



RBD, restless legs syndrome, obstructive sleep apnea, and insomnia [24]. A further study described the presumed presence of RBD in 12 of 22 (56%) SCA3 patients of Portuguese or Azorean origin [25]. These studies used only questionnaires, and this may have resulted in confusion of RBD with other parasomnias. As an illustration, in a SCA3 patient with clinically suspected RBD, video-polysomnography showed normal REM sleep atonia and non-REM sleep episodes of complex nonrhythmic behaviors lasting more than 10 minutes [26].

Several case reports of RBD with confirmed polysomnography have been reported in SCA3 patients [27–29]. We described the presence of video-polysomnography confirmed RBD in five of nine (55%) consecutive Spanish SCA3 patients, four men and one woman, with a mean age of 48 years and a mean ataxia duration of 14 years [30]. In two patients, RBD preceded the ataxia onset by 10 and 8 years, respectively.

In SCA2, a cerebellar syndrome characterized by CAG repeat expansion in the SCA2 gene with saccade slowing and gaze palsy [23], two studies have evaluated the presence of RBD by clinical history and polysomnography. One study evaluated eight patients from five German families with sleep interviews and video-polysomnography. All but one reported good-quality sleep. None of the patients and bed partners reported symptoms that might suggest RBD such as violent nightmares, frequent vocalizations, or aggression during sleep. Video-polysomnography, however, showed sub-clinical RBD (increased submental electromyographic activity not associated with abnormal behaviors) in three patients, normal REM sleep in two, and an apparent absence of REM sleep in three [31]. In another study, four of five SCA2 patients of three different Austrian families had increased electromyographic activity during REM sleep in the video-polysomnograph. These four patients exhibited a mild form of RBD consisting of prominent myoclonic jerks in absence of complex behaviors [32].

REM sleep behavior disorder has also been observed in SCA1 [33]. A 22-year-old man with Friedreich ataxia was recently demonstrated to have severe clinical RBD in which video-polysomnography showed abnormal vigorous behaviors mainly affecting the head and trunk during REM sleep (personal observation). By contrast, in one study, RBD was not detected in five patients with SCA6 [34].

If treatment of RBD in these disorders is appropriate, an approach mirroring that in parkinsonian disorders is suggested with clonazepam or melatonin as first-line drugs (see chapter 9).

### **Restless legs syndrome in hereditary ataxias**

Several studies have evaluated the occurrence of restless legs syndrome in subjects with the various SCA syndromes [30,32,34–38]. Significant restless legs syndrome was seen in patients with SCA1, SCA2, SCA3,

and SCA6 who were not treated with dopaminergic or antidopaminergic drugs (table 11.1). The highest frequency of restless legs syndrome has been found in SCA3, ranging from 30% to 55% of the observed cases [30,35–37], a proportion consistently higher than that seen in control populations. Polysomnography in SCA1, SCA2, SCA3, and SCA6 has generally revealed a high number of periodic leg movements in sleep (PLMS) in patients with or without restless legs syndrome [30,32,34,35,38]. Most SCA patients, however, were unaware of any significant leg movements and PLMS were not usually associated with arousals.

Results from one study [35] in 89 patients found restless legs syndrome in 2 of 11 (18%) SCA2 patients, 23 of 51 (45%) SCA3 patients, and 1 of 21 (5%) SCA6 patients, whereas none of the 6 SCA1 patients studied had symptoms. Restless legs syndrome was usually clinically severe and standard therapy with levodopa or a dopaminergic agonist was effective in 14 of 16 patients. A PLMS index greater than 15 was found in all the 7 SCA3 patients (6 of whom also exhibited restless legs syndrome) who underwent nocturnal polysomnography. The results of several other studies are summarized in table 11.1.

The etiology of restless legs syndrome in subjects with autosomal dominant SCAs is unknown. Peripheral neuropathy and length of the CAG repeat expansion have not been associated with restless legs syndrome in SCA1, SCA2, and SCA3 [35,36]. Conversely, in patients with idiopathic and familial restless legs syndrome no expanded CAG repeats were identified in the SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 loci [39,40].

Central dopaminergic dysfunction may be suspected given the reported response to levodopa in some subjects with SCAs [35,36]. Furthermore, in SCA3, there is established neurodegeneration in both the substantia nigra and basal ganglia [23]. Functional neuroimaging studies have also shown decreased transporter binding in the nigrostriatal dopamine pathway in patients with and without extrapyramidal signs [41], and decreased  $^{18}\text{F}$ -fluorodopa uptake in the putamen [42]. Furthermore, nigrostriatal dopaminergic impairment is suspected in SCA2, SCA3, and SCA6 since some patients develop parkinsonism that responds to levodopa and functional studies in these patients demonstrated reduction of presynaptic striatal dopamine transporters [43–47]. Interestingly, a functional neuroimaging study in SCA1, SCA2, and SCA3 patients with restless legs syndrome showed normal postsynaptic striatal D2 receptor availability in the striatum, suggesting that the postsynaptic striatal system is not clearly implicated in the development of restless legs syndrome [38].

### **Sleep disordered breathing in hereditary ataxias**

Generally, polysomnographic studies in patients with autosomal dominant SCAs [27–32,34] and ataxia telangiectasia [48] have shown that

**Table 11.1** Studies evaluating the frequency of restless legs syndrome in spinocerebellar ataxias

Reference	SCA1 (n)	RLS (%)	SCA2 (n)	RLS (%)	SCA3 (n)	RLS (%)	SCA6 (n)	RLS (%)	RLS in controls (%)
Schöls et al. 1998 [35]	6	0	11	18	51	45	21	5	–
Abele et al. 2001 [36]	13	23	22	27	23	30	–	–	10
Iranzo et al. 2003 [30]	–	–	–	–	9	55.5	–	–	0
Boesch et al. 2006 [34]	–	–	–	–	–	–	5	40	–
Boesch et al. 2006 [32]	–	–	5	0	–	–	–	–	–
Reimold et al. 2006 [38]	4	25	4	25	2	100	–	–	–
D’Abreu et al. 2008 [24]	–	–	–	–	53	20.7	–	–	4.7

RLS, restless legs syndrome; SCA, spinocerebellar ataxia type.

obstructive sleep apnea is not a common finding, although one study demonstrated an apnea-hypopnea index greater than 5 in four of five patients with SCA6 (range, 6–15) [34]. However, other sleep-related breathing problems may be important.

We evaluated sleep-disordered breathing in nine SCA3 patients by polysomnography and laryngoscopy during wakefulness. Stridor secondary to vocal cord abductor paralysis occurred in one patient who required emergency tracheotomy because of subacute respiratory failure. In two other patients, laryngoscopy disclosed partial vocal cord abduction restriction that was unilateral in a 57-year-old man with 14-year disease duration, and bilateral in a 63-year-old man with a 23-year disease duration. These two patients did not have stridor, dyspnea, or dysphonia, and polysomnography excluded obstructive sleep apnea. In the remaining six patients, the vocal cord movements were normal [30]. Vocal cord abductor paralysis has also been described in SCA1 [49]. This suggests impairment of the posterior cricoarytenoid muscle, the sole abductor of the larynx, which is innervated by the recurrent laryngeal nerve. Neuropathological changes in SCA3 patients with dysphonia include neuronal loss in the nucleus ambiguus [50]. Thus, vocal cord abductor dysfunction in SCA3 may result from neuronopathy of the nucleus ambiguus impairing the recurrent laryngeal nerve fibers that mainly innervate the posterior cricoarytenoid muscle. This is supported by the findings of a study showing neurogenic atrophy of the intrinsic laryngeal muscles in SCA3 patients with vocal cord abduction palsy [51].

### Key points

- In Alzheimer's disease, the sleep-wake cycle can be severely disturbed although there is no pathognomonic pattern. Medication side effects and sleep-disordered breathing may be important in individual patients.
- Patients suffering from dementia with Lewy bodies frequently have significant daytime somnolence and very disturbed nocturnal sleep with nocturnal confusion and REM sleep parasomnias as particular problems. Management approaches are the same as for severe parkinsonism.
- Huntington's disease may produce severe sleep-wake disturbance especially if advanced. Disorganization of circadian rhythm control appears most characteristic with advancement of the sleep phase and general sleep fragmentation as typical features.
- The well-described association of REM sleep behavior disorder with parkinsonian syndromes may also extend to the hereditary ataxias, especially SCA3 (Machado-Joseph disease).
- SCA3 may also predispose to restless legs syndrome.
- Sleep-related breathing disorders are not routinely seen in the hereditary ataxias although neurogenic vocal cord paralysis has been reported in SCA3 and SCA1.

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## **PART IV**

# Neuromuscular Disorders

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## CHAPTER 12

# Myotonic dystrophy

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### Introduction

Myotonic dystrophy (MD) is one of the most common inherited neuromuscular diseases in adults. Myotonic dystrophy is classified into two different types based on precise molecular diagnosis. MD type 1, the most frequent form, is caused by an unstable CTG repeat expansion in the 3' untranslated region of the DMPK gene on chromosome 19q13 [1]. MD type 2 or proximal myotonic dystrophy is related to a CTG expansion in the zinc finger protein 9 gene on chromosome 3q [2]. Both MD1 and MD2 are multisystem disorders with a common clinical picture but with subtle differences such as the age of onset and the precise pattern of muscle weakness. However, in contrast to MD2, the central nervous system is also affected by the degenerative process in MD1, as demonstrated by several neuro-imaging and neuropathological studies [3–6]. Based on this and on its higher prevalence, this chapter will primarily deal with MD1.

Sleep disorders are prevalent in MD1. In part, these can be caused by nocturnal disturbances, in particular sleep-related breathing disorders. In this respect, there is much in common with other neuromuscular disorders which are discussed in chapter 13. However, MD1 patients are often affected by an additional primary hypersomnia. In fact, excessive daytime sleepiness (EDS) is considered by some authors to be the most common clinical manifestation of the disease. A central hypersomnia is clearly unusual for a predominantly neuromuscular disorder and its diagnosis necessitates specific diagnostic attention as well as treatment.

## Clinical epidemiology

The prevalence of MD1 is approximately 1 in 8000. Age of onset and severity is directly correlated with the number of CTG repeats. Although longevity is not affected in many patients, many are increasingly disabled by the fifth or sixth decade after an insidious and long disease course. However, sudden death may occur in some cases secondary to cardiac arrhythmias.

The prevalence of specific sleep disorders in MD1 is poorly defined. In part, they clearly depend on the stage of the disease. For example, sleep-related breathing disorders are rare in early stages, becoming much more prevalent with disease progression. For EDS, prevalence has been reported variously between 33% and 77% [7–8], developing at any point along the clinical course of the disease.

## Signs and symptoms

Although usually characterized as a neuromuscular disorder, MD1 should be properly regarded as a multiorgan disease. Weakness and wasting predominantly affects the distal limbs and oropharyngeal musculature. Atrophy and weakness of the temporalis muscles, frontal baldness, ptosis, and a “long face” produce the characteristic facial appearance (figure 12.1). Myotonia is a core feature, most easily observed in the hands, and clinically manifest by an inability to release objects quickly. When formally assessed, mild cognitive impairment is common and motivational symptoms such as apathy are often apparent. Finally, cardiac (conduction) abnormalities are typical, and endocrine disturbances (testicular atrophy, insulin resistance) are often encountered.

## Nocturnal sleep disturbances

The quality of nocturnal sleep is very variable between patients, ranging from undisturbed and restorative sleep to frequent nocturnal awakenings and profound insomnia. The single most important cause of disturbed nocturnal sleep is a sleep-related breathing disorder (see chapter 13). This manifests itself in the usual way with snoring and witnessed apneas or gasping as common observations. Features often encountered in “primary” obstructive sleep apnea such as an increased neck circumference or a crowded oropharynx are less important factors in MD.

Other sleep disorders such as restless legs syndrome do not appear to have an increased prevalence in MD [8,9]. However, one should be cautious not to confuse restless legs syndrome with peripheral vascular



**Figure 12.1** Typical appearance of myotonic dystrophy type 1. Note the frontal baldness, bilateral ptosis, long face, and masseter atrophy. Photograph kindly provided by Dr J. Pascual, with written permission from the patient for publication.

symptoms such as coldness, episodic pallor of the distal limbs, or muscle pain, which are all commonly reported symptoms in MD1 [6,10].

### **Excessive daytime sleepiness**

EDS has been noted as one of the main clinical complaints of MD1, often preceding other systemic manifestations [11]. However, it is rare for this aspect of a patient's symptoms to be picked up early as many physicians typically pay little attention to sleepiness when taking a medical history. Conversely, if attending a sleep clinic, MD1 may be missed in the early stage, when physicians do not have this diagnosis in mind when assessing a patient with daytime sleepiness. In MD1, it is likely that EDS is often interpreted as lack of motivation, laziness, apathy, or loss of interest given that these traits seem common at any stage of the disease [7,12–14]. However, paradoxically, apathy may also be a reason patients do often not spontaneously complain of sleepiness per se. Indeed, it is common for relatives to notice excessive sleepiness and unplanned naps in subjects who, themselves, may appear unaware of any significant problem [12,15].

Clinically, the severity EDS in MD1 can be comparable to that seen in primary hypersomnias such as narcolepsy. On the background of fairly continuous excessive sleepiness during the day, sudden episodes of irresistible sleep or “sleep attacks” are a common manifestation. However,

there have been no reports of other symptoms of typical narcolepsy in MD1 such as cataplexy or REM sleep-related phenomena during the night.

Clinically, it may be difficult to distinguish EDS from the common complaint of fatigue in myotonic dystrophy. However, studies have shown these to be separable entities [13]. Unintentionally falling asleep during the day is the key to EDS, a feature not characteristic for fatigue.

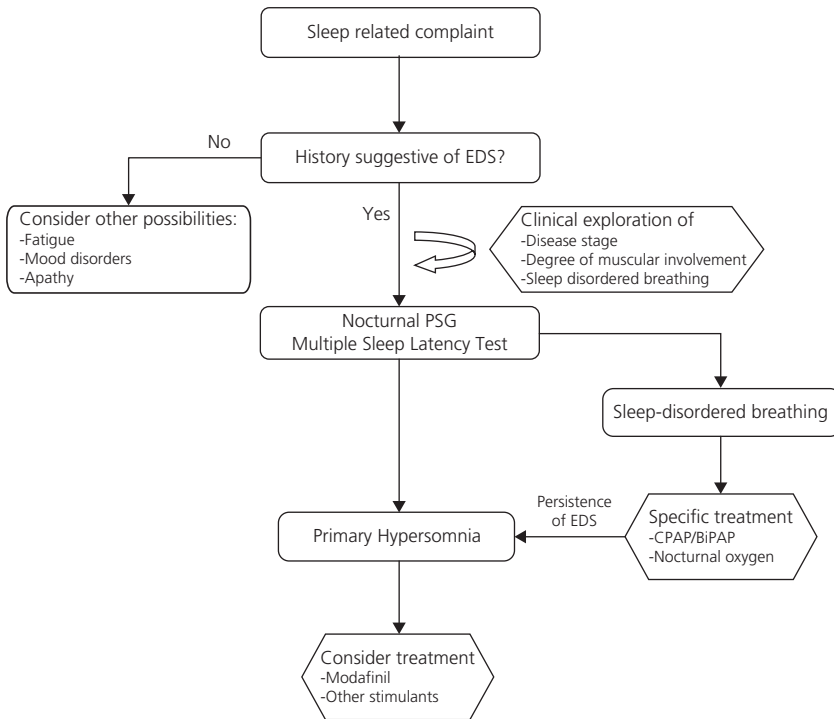
Although EDS may be secondary to sleep-related breathing disorders, the severity of sleepiness is only weakly correlated with the degree of muscular impairment [8,16]. Moreover, EDS often persists after appropriate treatment of the sleep-disordered breathing [17,18]. Similarly, other variables such as age, anthropometric data, gender, number of CTG repeats, or disease duration are not correlated with the severity of EDS. Therefore, EDS has been related to an intrinsic central dysfunction of the brain areas controlling the sleep-wake cycle that may be involved in the neurodegenerative process of MD1 [4,9]. Indeed, defects in hypothalamic hypocretin signaling in MD1 have been reported, although these results have not been confirmed in other studies [9].

## Diagnostic procedures

Because of the multiple potential etiologies of sleep-related symptoms in MD1, the patient should ideally be assessed in a sleep laboratory whenever the generalist suspects the presence of EDS, apneas, or other sleep disorders.

Figure 12.2 outlines the general procedure to follow in the evaluation of sleep disorders in a patient with MD1. As commented, the first step is to assess the possibility of potentially treatable causes such as sleep-disordered breathing. As a general rule, a MD1 patient cannot be diagnosed with central hypersomnia if a complete sleep study has not been performed first.

Every clinical interview in a MD1 patient with sleep-related symptoms should include questions on the presence of EDS (see chapter 1), indicators of sleep-disordered breathing (e.g. snoring and witnessed apneas), and any other nocturnal sleep disorders. In addition, clinical characteristics such as the degree of muscle involvement are important. Physicians should keep in mind that MD1 patients do not always recognize EDS as a medical problem. This may be one of the main reasons why common clinical scales used for assessment of EDS in other pathologies are of very limited value in MD1. For example, even those MD1 patients with objectively diagnosed EDS often score below the diagnostic threshold of the Epworth Sleepiness Scale (ESS), the most common



**Figure 12.2** Flow chart for the diagnosis and management of EDS in myotonic dystrophy type 1.

tool for the subjective exploration of daytime sleepiness. This is further accentuated by the fact that the ESS includes activities that many MD1 patients have to give up.

Formal sleep investigation should play a central role in the work-up of a MD1 patient with sleep-related complaints. Nocturnal polysomnography should always be performed, with a specific focus on the presence of sleep-related breathing disorders. When there is a complaint of EDS, a Multiple Sleep Latency Test (MSLT) can also be useful. This provides an objective evaluation of sleep propensity, and a useful starting point to initiate treatment. In addition to a mean sleep latency below 8 minutes, MD1 patients often show multiple sleep onset REM periods during the MSLT, analogous to narcolepsy [19]. This further emphasizes the potential role of the central nervous system in the generation of any hypersomnia. In the studies reporting low CSF hypocretin-1 levels in MD1 [9], only a subset of patients with EDS showed clearly decreased levels. Therefore, hypocretin-1 measurements are not generally useful in the clinical work-up of EDS in MD1, as the available polysomnographic techniques suffice.

## Management

Significant sleep-related breathing disorders always justify treatment, both for symptom control and because of the increased cardiovascular risk. First-line treatment is positive airway pressure, with conventional CPAP as a starting point. However, the use of CPAP may be limited by the degree of muscle weakness and bi-level positive airway pressure (BiPAP) therapy is regularly indicated. Oxygen therapy should always be considered in patients with significant nocturnal breathing disorders, although it should be used with caution, and preferably with input from a respiratory physician. Further details can be found in chapter 13.

If breathing disorders are not present, or when adequate treatment does not eliminate EDS, medical treatment can be considered. Before establishing chronic medical treatment for sleepiness, physicians should be aware that not all patients consider EDS as a “real” medical problem. However, pharmacological treatment with stimulants should be initiated in those patients with disability due to EDS. Both amphetamine-like stimulants and modafinil can be used to good effect in the treatment of EDS in MD1 [10,20,21].

Methylphenidate 10–40 mg is effective, but may be limited by side effects. Furthermore, tolerance has been observed in some patients [18]. Small open-label trials of modafinil (200–400 mg/day) showed that the drug is well tolerated and without significant side effects [21,22]. Positive clinical effects were corroborated by an increase in MSLT sleep latency in one study. Moreover, tolerance has not been reported with modafinil in MD1. Before starting any stimulant treatment in a patient with MD1, in view of potential cardiac complications, a cardiologist should be consulted and an appropriate work-up performed.

### Key points

- Excessive daytime sleepiness (EDS) can be a defining feature of myotonic dystrophy, particularly MD1, and may appear very early in the disease course.
- Sleep-related breathing disorders can be a significant cause of EDS, but often the hypersomnia is also of central origin.
- A partial deficiency of hypocretin may contribute to sleep-related symptoms.
- When EDS adversely affects daytime functioning of patients, treatment with stimulants is indicated and can be very rewarding.
- A thorough cardiac work-up before initiating stimulant treatment is strongly recommended in a patient with myotonic dystrophy.



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## CHAPTER 13

# Sleep and breathing in neuromuscular disease

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### Introduction

Sleep-disordered breathing is common in many neuromuscular conditions, particularly those associated with respiratory muscle weakness. Indeed, patients with severe muscle weakness often complain of unrefreshing nocturnal sleep, daytime sleepiness, fatigue, and impaired concentration directly due to nocturnal hypoventilation and/or sleep disruption. Abnormalities of breathing during sleep include episodes of apnea, brief hypopneas, and more prolonged periods of nocturnal hypoventilation. Each is typically associated with oxygen desaturation and all may disrupt sleep even before development of daytime ventilatory failure with hypercapnia [1,2]. The availability of effective treatment in the form of noninvasive ventilation (NIV) heightens the need to recognize the consequences of sleep-disordered breathing. Indeed, there is increasing evidence that nocturnal noninvasive ventilation can improve both the quality of life and survival of many patients with neuromuscular disease [3,4].

In this chapter, normal respiratory muscle activity and breathing during sleep are first described, followed by a brief review of the effects of various neuromuscular disorders on sleep architecture, sleep-disordered breathing, and nocturnal oxygenation. Finally, the abnormalities seen in some specific conditions and the impact of nocturnal noninvasive ventilation on sleep and breathing in patients with neuromuscular disease are discussed.

### Effect of sleep on breathing

The respiratory muscles and their output are controlled by two distinct neural pathways [5]. The so-called “metabolic” or automatic control

pathway originates from neurons with an inherent rhythmicity, located mainly in the pre-Bötzinger complex in the ventrolateral medulla. These act as the “pacemaker” for regular tidal breathing and their efferent connections to the spinal motor neurons are via the bulbospinal pathways in the ventrolateral spinal cord. A second, so-called “behavioral,” control system allows the metabolic pathway to be overridden during voluntary acts such as speech, breath-holding, etc. This neural pathway originates in the cerebral cortex and descends via the reticular formation and the corticospinal tracts in the dorsolateral columns to the spinal motor neurons. When awake, a “wakefulness drive” exerts a stabilizing influence which tends to maintain adequate ventilation but, when this is lost during sleep, any perturbation of the negative feedback system from the chemoreceptors can destabilize breathing. If this happens the automatic control system is liable to overshoot, resulting in periodic breathing, with periods of hyperpnea alternating with hypopnea. This occurs in healthy individuals at sleep onset and at altitude and, in disease, may be manifest as Cheyne-Stokes breathing. During the deeper stages of non-REM sleep, behavioral influences are minimal and ventilation is most dependent on the automatic control system. Consequently, if the latter is damaged by disease, breathing may be grossly disturbed especially during slow-wave sleep, even though, when awake, behavioral control and the wakefulness drive may compensate sufficiently to maintain adequate ventilation.

Sleep is accompanied by an important increase in the resistance of the pharyngeal airway. This results from a sleep-related decline in the tonic activity of the pharyngeal dilator muscles which support the upper airway during inspiration. In non-REM sleep, particularly slow-wave sleep, breathing is characteristically regular, but overall ventilation is reduced by about 15% compared to wakefulness.

During REM sleep, breathing is more variable and irregular, particularly during the brief periods of phasic eye movements which punctuate REM sleep. Respiratory muscles other than the diaphragm share the general hypotonia of skeletal muscles which accompanies REM sleep. Upper airway dilator muscles are therefore affected and the consequent loss of pharyngeal support makes the airway more compliant (“floppy”), contributing to a greater frequency of obstructive apneas and hypopneas during REM sleep. Individuals whose ventilation is compromised, from whatever cause, are therefore particularly vulnerable during REM sleep, and the ventilation of patients with severe diaphragmatic weakness or paralysis is likely to be even more precarious at this time.

In healthy individuals, the overall reduction in ventilation during sleep leads to a small fall in arterial oxygenation, with mean nocturnal values of oxygen saturation ( $\text{SaO}_2$ ) about 2–3% less than awake values. There is a small reciprocal rise in arterial  $\text{PCO}_2$  ( $\text{PaCO}_2$ ). Compared to oxygen, there are much larger body “stores” of  $\text{CO}_2$  and these act as a buffer which

dampens the tendency for  $\text{PaCO}_2$  to increase during short periods of apnea or hypopnea. However, the overall hypoventilation during sleep results normally in a slightly higher  $\text{PaCO}_2$  (typically by 0.5–1.0 kPa) in the early morning compared to values later in the day.

With full or partial arousal from sleep, transient hyperventilation occurs by a reflex effect. This is essentially a defence mechanism which ensures the maintenance or re-initiation of ventilation after a period of apnea, for example.

## **Respiratory muscle weakness and sleep architecture**

Patients with ventilatory compromise due to respiratory muscle weakness often have reductions in total sleep time and/or efficiency, with varying degrees of sleep fragmentation, frequent arousals, an increased proportion of stage 1 sleep, and reduction in REM sleep [1]. Complete suppression of REM sleep has been reported in some patients with severe diaphragmatic weakness. Since the ventilation of such individuals is particularly vulnerable during phasic REM sleep, this may, in fact, represent a compensatory mechanism. For a given impairment of respiratory function there is considerable variation in the degree of sleep disruption and this may account for some of the wide variation in symptoms between patients [6].

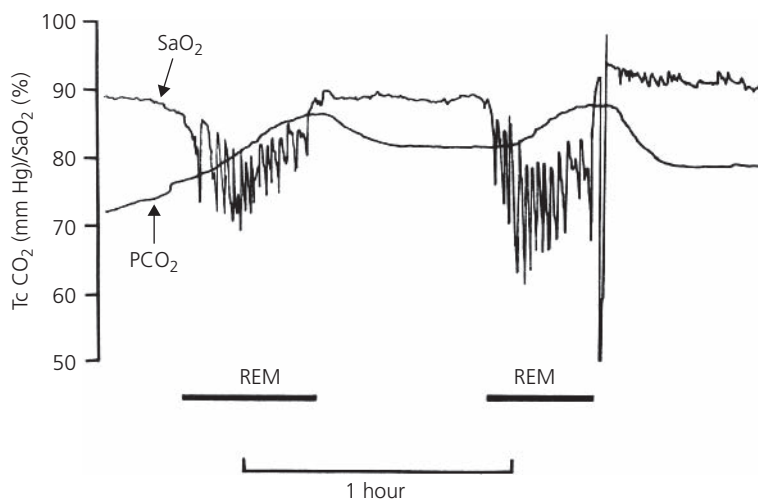
## **Patterns of sleep-disordered breathing in neuromuscular disease**

Conventionally, periods of apnea and hypopnea are defined as discrete episodes lasting at least 10 seconds, with apneas classified as “central” or “obstructive” depending on whether or not persisting respiratory effort is detectable. However, classification of such episodes can be difficult in patients with neuromuscular disease, especially if conventional methods of noninvasive monitoring are employed. In particular, obstructive apnea can be misdiagnosed as “central” when the respiratory muscles are too weak to produce chest wall movement in the face of a closed upper airway. In this situation, inspiratory muscle EMG activity may still be detectable and such apneas have been described as “pseudocentral.” Classification of hypopneas may be even more problematic, as severe diaphragmatic weakness can cause paradoxical movement of the ribcage and abdomen, a feature which in other circumstances is regarded as suggestive of an obstructive sleep-breathing event. In this context, the simple clinical recognition of snoring is often good evidence for an obstructive etiology.

The most common discrete abnormalities of breathing in patients with respiratory muscle weakness are central hypopneas. These are

most frequent and prolonged during periods of rapid eye movements in REM sleep (phasic REM) [7]. The hypopneas result from suppression of intercostal and accessory respiratory muscles, together with inadequate diaphragmatic recruitment; the consequent reduction of ventilation is proportional to the density of eye movements. This results in the characteristic picture of REM-related oxygen desaturation, which is often seen with overnight oximetry recordings in patients with respiratory muscle weakness (figure 13.1). Predominantly obstructive apneas or hypopneas are seen in a minority: these are more likely in individuals who snore, those with a higher body mass index, or those who have other factors, including macroglossia, which predispose to pharyngeal obstruction.

As respiratory muscle weakness progresses, sleep-related hypopneas increase and the pattern merges with more sustained hypoventilation [2]. The distinction between hypopnea and hypoventilation is, however, essentially semantic and depends on whether brief discrete episodes of reduced ventilation are identifiable, with a return to relative normality between events. In more severely affected individuals the clue to persistent hypoventilation from an oximetry recording is a low “baseline”  $\text{SaO}_2$ , on which periodic dips are superimposed (figure 13.1). In general, the hemoglobin-oxygen dissociation curve dictates that the lower the starting  $\text{SaO}_2$ , the larger the dip following a period of apnea or hypopnea.



**Figure 13.1** Example of arterial oxygen saturation ( $\text{SaO}_2$ ) and transcutaneous  $\text{PCO}_2$  ( $\text{Tc CO}_2$ ) during sleep in a patient with respiratory muscle weakness due to acid maltase deficiency. During two periods of REM sleep, repetitive falls in  $\text{SaO}_2$  are seen corresponding to periods of phasic eye movements.  $\text{PCO}_2$  shows a gradual rise during each REM period, implying more severe hypoventilation. Note the low baseline  $\text{SaO}_2$  and persistently elevated  $\text{PCO}_2$ , implying chronic hypoventilation. Reproduced with permission from reference [8].

The apnea/hypopnea index (AHI), as conventionally used in patients with the obstructive sleep apnea syndrome, is thus an inadequate descriptor of the severity of sleep-disordered breathing in this population, at least in those with more severe respiratory muscle weakness.

## **Relations between diurnal respiratory function and nocturnal oxygenation**

Nocturnal oxygen saturation correlates with daytime  $\text{SaO}_2$  or  $\text{PaO}_2$ , and, inversely, with daytime  $\text{PaCO}_2$  [8]. In general, if arterial oxygenation is low when the individual is awake, the breathing-related falls in  $\text{SaO}_2$  when asleep are amplified. In those with milder weakness, nocturnal desaturation and nocturnal hypercapnia may be detectable before daytime respiratory failure develops, and sleep studies may therefore be more sensitive for identifying abnormal respiratory function than are daytime blood gas measurements [9]. In general, however, the more severe the mechanical abnormality, as assessed by simple measurements such as vital capacity, the more abnormal is gas exchange during sleep, although correlations are relatively weak and nonlinear [1]. Polysomnography allows recognition of the occasional individuals in whom obstructive apneas are predominant, but whether patients with respiratory muscle weakness should be monitored routinely by sleep studies is not clear, as the value of early detection of sleep-disordered breathing has not been established. On the contrary, studies of the effects of respiratory function on survival in neuromuscular disease have consistently shown that simple daytime measurements such as vital capacity, maximum inspiratory pressure, or awake arterial blood gases are better predictors of prognosis than nocturnal measurements [10,11]. Similarly, when predicting the benefit of treatment with noninvasive ventilation, daytime respiratory function plus symptoms (sleepiness, orthopnea) are superior to measurements during sleep [12].

## **Specific disorders**

Some of the neuromuscular conditions more commonly associated with sleep hypoventilation and chronic hypercapnic respiratory failure are listed in table 13.1. The cause may reside at any level in the neuromuscular control system. The final common pathway is inadequate output by the respiratory muscles, but this can result from failure of respiratory drive in the brainstem, interruption of the neural pathway at upper or lower motor neuron levels, or disease primarily affecting the muscles themselves. The common symptoms of fatigue, sleepiness, impaired concentration, and morning headaches may reflect either chronic ventilatory failure, with

**Table 13.1** Neuromuscular conditions associated with hypercapnic respiratory failure and sleep hypoventilation

Brainstem	Congenital central hypoventilation syndrome (“Ondine’s curse”) [13] Neoplastic/vascular lesions Arnold-Chiari malformation [14]
Spinal cord	Cervical cord trauma [15] Post cordotomy [16]
Motor neurons	Poliomyelitis [17] Amyotrophic lateral sclerosis [18,19]
Peripheral nerves	Guillain-Barré syndrome [20]
Motor end plate	Myasthenia gravis [21] Lambert-Eaton syndrome [22]
Respiratory muscles	
Specific	Bilateral diaphragmatic paralysis (e.g. neuralgic amyotrophy) [23]
Generalized	Duchenne muscular dystrophy [9] Late-onset dystrophies [24] Polymyositis [25] Mitochondrial myopathies [26] Metabolic myopathies (e.g. acid maltase deficiency) [27] Myotonic dystrophy [28]

persistent hypercapnia, or may simply result from sleep disturbance and disruption. In many cases both mechanisms apply.

### Central hypoventilation syndromes

Congenital central hypoventilation syndrome (“Ondine’s curse”) is a rare condition characterized by chronic hypoventilation which becomes most evident during non-REM sleep when the automatic respiratory control system is usually dominant. Most cases are recognized shortly after birth although some also present in later childhood or even in adult life [13]. The syndrome is inherited as an autosomal dominant trait and is related to a mutation of the PHOX2-B gene which also has an important role in the development of the autonomic nervous system. Central hypoventilation may also be acquired, as a result of infections such as poliomyelitis, cerebrovascular disease including stroke, or brainstem tumors.

Daytime hypercapnic respiratory failure and sleep hypoventilation or central sleep apnea are well-recognized consequences of the Arnold-Chiari malformation [14] secondary either to compression of the medulla by herniation through the foramen magnum or to an associated syrinx interrupting the reticulospinal pathways which mediate the “metabolic” respiratory control system. Sleep-disordered breathing improves in some patients after decompressive surgery.

### Spinal cord lesions

The effects of traumatic cervical cord injury on respiratory function depend critically on the level of the damage. Transection above the



phrenic nerve outflow, at the C1 or C2 level, causes paralysis of all the main respiratory muscles, with apnea, followed rapidly by death unless ventilatory support is instituted. Lesions of the lower cervical cord leave the diaphragm and inspiratory accessory muscles unaffected although inspiratory intercostal and most expiratory action is impaired or lost. As a consequence, sleep-disordered breathing is common in the first few weeks after cervical cord injury [15].

Central sleep apnea and hypoventilation are well-recognized complications of bilateral cervical cordotomy for relief of intractable pain [16]. This procedure, which involves interruption of the ascending spinoreticular pathways, may be accompanied by damage to the adjacent descending reticulospinal tracts which mediate the automatic respiratory control system. Unexpected postoperative death during sleep, probably due to central apnea, has been reported.

### **Motor neuron diseases**

Acute poliomyelitis can result in respiratory failure by affecting either the medullary respiratory centers or spinal motor neurons. Late effects are also increasingly seen in long-term survivors with the "post-polio" syndrome. This is associated with progressive respiratory muscle weakness, particularly in those whose respiratory muscles were affected at the time of the original illness. Nocturnal hypoventilation may result along with apneas which may be either central or, sometimes, obstructive [17].

Sleep studies in patients with motor neuron disease (amyotrophic lateral sclerosis, ALS) often show abnormalities, particularly REM-related hypopnea and oxygen desaturation with underlying hypoventilation in those with more severe respiratory muscle weakness. Nocturnal desaturation and sleep disruption are more likely to be due to respiratory muscle weakness and hypoventilation than to clinically obvious bulbar weakness [18,19].

### **Peripheral nervous system**

In inflammatory neurological conditions such as Guillain-Barré syndrome, weakness can progress rapidly over weeks or days with significant involvement of respiratory muscles in around a third causing weakness sufficiently severe to require ventilatory assistance [20]. Similar levels of weakness producing chronic hypercapnic respiratory failure is also seen occasionally in the hereditary neuropathies.

### **Motor end plate**

REM sleep-related oxygen desaturation is well recognized in advanced myasthenia gravis. Frank obstructive sleep apnea is reported in some patients, presumably due to weakness of the upper airway muscles [21].

Weakness sufficient to cause hypercapnic respiratory failure is also seen occasionally in the myasthenic Lambert-Eaton syndrome [22].

### **Diaphragm**

In most neuromuscular conditions affecting the respiratory muscles, weakness is global. Occasionally, however, isolated bilateral diaphragmatic paralysis (BDP) is seen. Among the commoner causes is neuralgic amyotrophy (brachial neuritis) affecting the C3–C5 nerve roots. The resulting diaphragmatic paresis may be unilateral or bilateral, either simultaneously or sequentially. The results of sleep investigations in patients with BDP are variable, with some, though not all, authors reporting sleep-related hypercapnia. Oxygen desaturation is more consistently seen, especially during REM sleep. Some patients with severe diaphragmatic weakness appear to adapt by suppressing REM sleep but others appear able to maintain a normal proportion of REM sleep through an unclear mechanism [23].

### **Generalized muscle weakness**

Sleep-disordered breathing is frequent in advanced Duchenne muscular dystrophy with periods of hypopnea and/or apnea. These are usually central in origin but may also be obstructive or pseudocentral, possibly due to hypertrophy of the tongue [9]. Indeed, chronic hypoventilation is virtually inevitable if patients survive long enough. Respiratory muscle weakness sufficient to cause hypercapnic respiratory failure is also seen occasionally in patients with late-onset dystrophies [24]. Many rarer congenital and acquired muscle diseases can affect the respiratory muscles sufficiently to lead eventually to hypercapnic respiratory failure. Among the more common are polymyositis [25], mitochondrial diseases [26], and acid maltase deficiency [27]. The last is relatively unusual among neuromuscular diseases in that the respiratory muscles often appear to be disproportionately affected such that severe diaphragmatic weakness or paralysis is relatively common and closely associated with sleep-disordered breathing and chronic hypercapnia.

### **Myotonic dystrophy**

Both daytime hypercapnia and sleep-disordered breathing are common in advanced myotonic dystrophy. Although previously attributed to an abnormality of central respiratory control, daytime hypercapnia correlates with the severity of respiratory muscle weakness in myotonic dystrophy in similar fashion to other muscle diseases [28]. Episodes of sleep apnea and hypopnea are also frequently found and may be either central or obstructive. Obesity is commoner in patients with myotonic dystrophy than in other neuromuscular conditions associated with respiratory

muscle weakness and the frequency of obstructive events during sleep correlates with BMI. Daytime somnolence is a major feature of patients with this condition. Although hypercapnia and/or sleep-disordered breathing may contribute in occasional individuals, it appears that these are not the main cause of sleepiness in the majority and a central cause is more likely (see chapter 12).

## **Treatment of sleep-disordered breathing in neuromuscular disease**

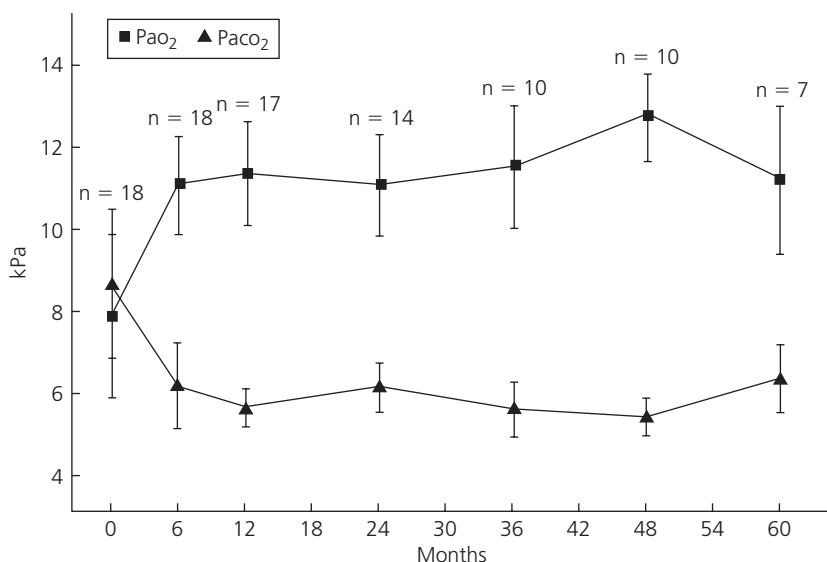
### **Oxygen and drugs**

In general, any individual with a high  $\text{PaCO}_2$  is at risk of worsening hypercapnia if treated by either uncontrolled oxygen or sedative agents including narcotic drugs. This applies to patients with advanced chronic obstructive pulmonary disease (COPD) and severe scoliosis as well as to those with severe respiratory muscle weakness. In the latter situation, the potential problem is best documented with uncontrolled oxygen, even at low flows, which can produce life-threatening increases in  $\text{PaCO}_2$  in patients breathing spontaneously [29]. Although less well documented, common clinical experience shows that strong sedation has a potentially similar effect, but, as with COPD, the danger is much less if  $\text{PaCO}_2$  is normal [30]. Such drugs are, of course, widely and appropriately used in palliative care for relief of severe breathlessness in pre-terminal patients where the risks are usually outweighed by the benefits.

Respiratory stimulant drugs such as doxapram are generally contraindicated in patients with neuromuscular disease and respiratory muscle weakness, with the exceptional situation of nalorphine when needed to counter the injudicious use of opiates.

### **Noninvasive ventilation**

Nocturnal noninvasive ventilation via a tight-fitting, usually full face mask or other interface has become standard treatment for hypercapnic respiratory failure and sleep-disordered breathing in selected patients with most of the conditions discussed in this chapter. The treatment is equally effective whether the hypoventilation results from inadequate respiratory drive or failure of the effector muscles themselves. In patients with established ventilatory failure, considerable improvement is seen, not only in nocturnal measurements, but also in daytime symptoms and arterial blood gases (figure 13.2). An increased blood concentration of bicarbonate ions has a depressant effect on ventilation and the improvement in daytime  $\text{PaCO}_2$  is probably due to the reduction in blood bicarbonate concentration which accompanies better nocturnal ventilation.



**Figure 13.2** Sustained improvement of *daytime* arterial PO<sub>2</sub> and PCO<sub>2</sub> in a group of patients with chronic respiratory failure due to Duchenne muscular dystrophy treated for up to 5 years with nocturnal NIV. Reproduced with permission from reference [3].

Effective use of this form of treatment requires careful attention to detail, particularly in relation to choice of interface. A variety of nasal, oral and oronasal interfaces is available and the choice in an individual is often a matter of trial and error. Weakness of facial and buccal muscles may exacerbate any tendency to leakage, thereby reducing efficacy and in itself causing sleep disruption. In most patients a simple bi-level pressure support ventilator is adequate in which the inspiratory and expiratory pressures are titrated against overnight SaO<sub>2</sub> recordings and patient reports of sleep quality. In the absence of coexistent pulmonary disease, ventilation with air usually suffices but, occasionally, supplementary oxygen is used via the ventilator. Even in severe ventilatory failure oxygen can be given safely once the patient is also receiving ventilatory support of this type.

Long-term supervision by an experienced team is essential for the success of noninvasive ventilation and patients require rapid access in the event of equipment failure. Although not usually regarded as a form of life support, a back-up source of power is desirable for those with the most compromised respiratory function.

Nocturnal noninvasive ventilation is well established in individuals with stable or only slowly progressive disease but its value was less clear in patients with a more limited prognosis such as those with ALS. However, a recent randomized controlled trial has confirmed improvements in both survival and quality of life in patients with ALS without severe bulbar dysfunction [4]. Patients with more severe bulbar impairment usually show

less good tolerance of noninvasive ventilation and benefits are less predictable. In general, the indications for treatment are daytime symptoms and chronic hypercapnia rather than any specific sleep-related symptoms or measurements. Some patients benefit from noninvasive ventilation even without daytime hypercapnia, in which case severe orthopnea is a particularly useful indicator for a trial of treatment [12]. Orthopneic patients may benefit because using noninvasive ventilation allows sleep in a more natural posture with less disruption, thereby improving daytime symptoms.

In myotonic dystrophy, noninvasive ventilation may be helpful in some patients with severe weakness and hypercapnia but the acceptability and benefit of this form of treatment is generally much less than in other conditions associated with a comparable degree of respiratory muscle weakness [31].

### Key points

- Sleep-disordered breathing (SDB) and/or daytime ventilatory failure (hypercapnia) can result from disease at various levels in the respiratory control pathway, including the brain stem, spinal cord, motor neurons and the effector muscles themselves.
- The breathing of patients with respiratory muscle weakness is most vulnerable during (phasic) rapid eye movement (REM) sleep, when the activity of most respiratory muscles is profoundly suppressed.
- Although measurements during sleep are more sensitive than tests of respiratory function awake, the prognosis for survival relates better to simple awake measurements such as vital capacity, maximum respiratory pressures and arterial blood gases. In the absence of sleep-related symptoms, routine sleep studies are not generally recommended.
- Nocturnal noninvasive ventilation (NIV) is now standard treatment for hypercapnic respiratory failure and sleep-disordered breathing in symptomatic patients with neuromuscular disease.

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## **PART V**

# Paroxysmal Neurology

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## CHAPTER 14

# Headache disorders

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### Introduction

Paradoxically, the state of sleep has long been recognized to provoke as well as relieve headache. With respect to the former possibility, clinical research has confirmed the comorbidity of several sleep and headache disorders, generally linking sleep disorders with more frequent and severe headaches. Nonspecific headache patterns including chronic daily “awakening” or morning headaches can serve as effective general markers for many sleep disorders. Snoring and other indicators of obstructive sleep apnea (OSA) are the most frequently studied areas. These are particularly salient because of associated morbidity as well as the potential positive impact treatments may have on headache management – anecdotal evidence suggests headache may improve or resolve with treatment of OSA. Other sleep disorders have been less frequently examined, but available evidence finds virtually every sleep disorder studied is more prevalent among individuals with headache than those without.

In addition to overt sleep disorders, clinical research has often revealed a close correlation between certain headache diagnoses (e.g. hypnic, cluster, migraine) and chronobiological patterns related to the sleep-wake cycle. Furthermore, acute sleep dysregulation such as sleep deprivation, oversleeping, and abrupt shifts in sleep schedule are among the most commonly identified “triggers” in migraine and tension-type headache. Accordingly, behavioral sleep modification to optimize sleep quality and duration has been shown to improve chronic migraine. Of relevance, it is believed that common neurobiological pathways, mostly in the hypothalamus, are involved in sleep regulation and generation of certain headache syndromes such as cluster headache.

Evidence supports routine screening for sleep disorders by headache practitioners and suggests sleep clinicians should familiarize themselves with headache syndromes. This chapter highlights pertinent primary and secondary headache diagnoses for which there is an empirical relation to sleep both from epidemiological and screening data. Diagnosis and management of sleep-related headache are also discussed.

## **Clinical epidemiology**

As reviewed elsewhere [1,2], virtually all sleep disorders examined to date are more prevalent among individuals with headache than those without headache. These associations tend to be greatest in chronic daily, morning, or awakening headache patterns. Awakening headache occurs in 4–6% of the population, 18% of insomniacs, between 18 and 60% of sleep apneics and 21% of depressed individuals across studies [2,3].

### **Sleep-disordered breathing**

Headache occurs more commonly among snorers and OSA than among non-snorers in adults as well as children [2]. For example, a cross-sectional study in Sweden [4] compared OSA subjects ( $n = 324$ ) to a random sample of the population divided into snorers ( $n = 448$ ) and non-snorers ( $n = 583$ ). They found that heavy snorers, both men and women, were more likely than non-snorers to have “headache at least once a week” or “morning headache.” Likewise, a case-control study in the United States, aimed at identifying risk factors for chronic daily headache [5], revealed that daily snoring was twice as common among 206 chronic daily than among 507 episodic headache sufferers. The risk rose to threefold after adjusting for traditional risk factors for OSA (i.e. age, gender, body mass index, alcohol intake, hypertension). The relationship was not accounted for by other factors such as caffeine consumption and depression.

The prevalence of OSA in unselected headache patients presenting for treatment has never been systematically assessed. However, based on relative risk identified in epidemiological research, OSA is almost certainly under-recognized in headache populations. At least two clinical subgroups appear at risk for OSA – cluster and chronic headache patients resistant to standard treatment. A study of 37 cluster headache patients who underwent polysomnography identified a 4-fold increase in the incidence of OSA relative to age- and gender-matched controls (58% versus 14% respectively) and this risk increased over 24-fold among patients with a body mass index (BMI)  $> 25 \text{ kg/m}^2$  [6]. Another uncontrolled study of 31 cluster headache patients who underwent polysomnography observed OSA in 80% (25/31) of these patients [7]. Likewise, Mitsikostas identified

OSA in 29% (21/72) of severe headache patients who were refractory to standard treatments and with various diagnoses including medication overuse and cluster headache [8].

### **Insomnia**

Evidence suggests a dose-response relationship between disturbed sleep and headache severity. For example, a cross-sectional study in the United Kingdom identified a relationship between headache severity and general sleep-related symptoms (e.g. trouble falling or staying asleep, feeling tired or worn out) [9]. Controlling for anxiety and depression, Vgontzas et al. also confirmed the association of sleep problems (trouble falling asleep, inadequate sleep) with migraine [10].

Although chronic insomnia is the most common sleep complaint among clinical populations affecting around 15%, it is particularly prevalent in headache sufferers. Kelman's descriptive study of 1283 migraineurs presenting for treatment to a specialty headache clinic found the majority of patients reported difficulty initiating (53%) and maintaining sleep (61%) [11]. Chronically shortened sleep patterns (< 6 hours/night) were observed in 38% of migraineurs and those migraineurs exhibited more frequent and severe migraine than individuals sleeping 6 to 8 hours. Findings were consistent with Calhoun's sample of 147 women with chronic migraine: 66% reported sleep-onset insomnia, 52% reported using sleeping pills, 63% reported napping, and a striking 84% reported feeling unrefreshed upon awakening [12]. While these two studies were retrospective and lacked a control group, they are likely to be representative of neurology or specialty headache practices, and are consistent with the clinical impressions of practitioners treating chronic migraine.

### **Circadian rhythm disorders**

Circadian rhythmicity has been identified in migraine [13], cluster [7,14], and hypnic [14,15] headache. Furthermore, a European epidemiological study suggested that "chronic morning headache" was twice as prevalent in circadian rhythm disorders and that the relationship strengthened when the data were reanalysed in a model that included only "daily" morning headache [16].

### **Other sleep disorders**

A case-control study in Germany assessed the prevalence of restless leg syndrome (RLS) in 411 migraine patients compared to 411 age- and sex-matched controls [17]. RLS was more frequent in migraine (17.3%) compared to controls (5.6%). There was a co-association with depression, with higher depression scores among migraineurs with RLS than those without RLS. Likewise, epidemiological studies indicate parasomnias

(e.g. nightmares, bruxism, sleepwalking) are approximately twice as prevalent in adults with chronic headache [16] and children with migraine and other headaches [18] than in those without headache.

Signs and symptoms

The *International Classification of Headache Disorders* 2<sup>nd</sup> edition (ICHD-II) includes two sleep-related headache diagnoses, “Sleep apnea headache” (table 14.1) and “Hypnic headache,” and lists sleep disturbance among symptoms of anxiety disorders that may be associated with headache [14].

Sleep apnea headache

ICHD-II classifies sleep apnea headache under “Headache attributed to hypoxia or hypercapnia” although authors have acknowledged the mechanisms and specificity of apnea to headache remains uncertain [14]. It is not clear if the pathogenesis is in fact hypoxemia or hypercapnia (as presently designated), or alternately some correlated but nonspecific consequence of the OSA (e.g. autonomic arousal, sleep dysregulation), since nonrespiratory sleep disorders are also associated with headache [2,3]. Diagnostic criteria have not yet been validated and data indicates OSA headache may present: as migraine, tension, cluster or unclassifiable; bilateral (52.6%) or unilateral (47.4%); location frontal (33.3%), frontotemporal (27.8%) or temporal (16.2%); pressing/tightening pain (78.9%); with intensity mild (47.4%), moderate (36.8%), or severe (15.8%) [19]. Headaches remit within 30 minutes

**Table 14.1** International Headache Society diagnostic criteria for sleep apnea headache [14]\*

- 
- A** Recurrent headache with at least one of the following characteristics and fulfilling criteria C and D:
    - 1 Occurs on > 15 days per month
    - 2 Bilateral, pressing quality and not accompanied by nausea, photophobia or phonophobia
    - 3 Each headache resolves within 30 minutes
  - B** Sleep apnea (Respiratory Disturbance Index  $\geq$  5) demonstrated by overnight polysomnography
  - C** Headache is present upon awakening
  - D** Headache ceases within 72 hours, and does not recur, after effective treatment of sleep apnea
- 

\*Sleep apnea headache is coded as a secondary headache – new onset headache or marked exacerbation of a primary headache by another disorder occurring in close temporal relation, known from good scientific studies to be capable of causing the headache, and headache remission follows cure or treatment of the underlying disorder – under the major classification “Headache attributed to disorder of homeostasis” and subclassification of “Headache attributed to hypoxia or hypercapnia.”

in 40% of cases and there is some evidence for a dose-response relationship between the severity of apnea (e.g. apneic events, oxygen desaturation) and headache [20].

### **Hypnic headache**

By definition, hypnic headache is confined to sleep and is known to occur in the mid to latter portion of the night. Because of the tendency to occur at approximately the same time each night, hypnic headache has been called “alarm clock” headache. Onset is after age 50 years and women are more commonly affected than men. Metaanalysis of data pooled from 71 cases of hypnic headache published in medical literature revealed an average duration of  $67 \pm 44$  minutes, frequency of  $1.2 \pm 0.9$  per each 24 hours, 60% were bilateral and usually moderate in severity [15]. Most (77%) reported headache between 120 and 480 minutes after sleep onset during the nocturnal sleep period and uncommonly during daytime naps. Anecdotal reports suggested an association between hypnic headaches and OSA or REM-related oxygen desaturations.

### **Cluster headache**

Arguably, every patient with cluster headache should be screened for sleep apnea. Cluster headache is more common in men and produces severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes if untreated. Distinct circadian and, in some cases, circannual patterns have been reported with 75% of episodes occurring between the hours of 9:00 pm and 10:00 am. Clusters occur in series for several weeks or months separated by remissions of several months or even years [14]. As noted above, cluster headache patients exhibited 8.4-fold incidence of OSA relative to age- and gender-matched controls, and 24-fold greater incidence among patients with a BMI > 25 [6].

### **Sleep-related headache triggers**

Among migraine and tension-type headache patients, sleep dysregulation (e.g. sleep disturbance, sleep loss, oversleeping) is the most frequently cited acute “headache trigger,” second only to stress, a relationship confirmed prospectively in time-series analysis [2]. Either chronically short or long sleep patterns have also been associated with chronic migraine. The Kelman study [11] described the association of sleep duration and migraine severity in 1283 patients; 398 short (<6 hours/night) sleepers exhibited greater headache frequency than 573 normal (6 to 8 hours) sleepers [17.6 vs 15.1 days/month]. Headache frequency for a small group of 73 long sleepers (>8 hours/night) was 17.5 headache days/month – similar to short sleepers, although the trend was not statistically significant. This U-shaped association of sleep duration and headache is

strikingly similar to that between sleep duration and mortality as well as sleep duration and risk of certain medical illness.

## Diagnostic procedures

Diagnosis begins with a thorough clinical interview, examining the headache history and patterns in relation to the sleep-wake cycle. History may be supplemented by quantitative data from questionnaires, prospective diary, and polysomnography.

### Sleep history

Overview of the 24-hour sleep-wake history includes: pre-sleep routine, sleep period (sleep latency, duration of sleep relative to time in bed, mid-cycle and early morning awakenings), nocturnal symptoms (e.g. respiratory, movement, waking), daytime functioning (e.g. napping, alertness versus sleepiness, fatigue), and behavioral measures or substances to promote sleep or wake. Useful information may be obtained not only from the patient, but also from the spouse or other observers. Patients who complain of insomnia should be questioned about factors known to undermine sleep:

- 1 bedroom environment which is not conducive to sleep (i.e. light, noise, television, computer or other stimulation);
- 2 an irregular sleep schedule;
- 3 napping or “resting” during the day; and
- 4 medications and substances (e.g. caffeine, alcohol, nicotine).

Table 14.2 includes basic questions that are considered clinically useful by the authors, though not empirically validated.

### Predictive equations

Risk for OSA may be estimated using tools such as the Berlin Sleep Questionnaire. This identified high versus low risk patients for OSA in the primary care environment (sensitivity 86%, specificity 77%, positive predictive value 89%, likelihood ratio 3.79) based on patient's neck circumference, habitual snoring or witnessed apnea, and hypertension [21].

### Standardized questionnaires

Questionnaires are available for a wide range of conditions (e.g. insomnia, restless legs, sleepiness, quality of life) [2]. The Epworth Sleepiness Scale (ESS) has been validated against objective polysomnographic measures of the propensity to fall asleep [22]. A quantitative (subjective) score for sleepiness can be compared to normative data for various sleep disorders and normal controls.



**Table 14.2** Headache practitioner’s brief sleep questionnaire\*

---

Name: \_\_\_\_\_

Today's date: \_\_\_\_\_ Your age: \_\_\_\_\_ Your gender (M/F): \_\_\_\_\_

a) My ideal amount of sleep is \_\_\_\_\_ hours (number of hours sleep you need each night in order to feel and function your best).

1 During the weekdays I usually:	2 During the weekends I:			
Go to bed at _____ AM or PM (time)	Go to bed at _____ AM or PM (time)			
Get up at _____ AM or PM (time)	Get up at _____ AM or PM (time)			
Sleep _____(total hours)	Sleep _____(total hours)			
b) I awaken from sleep with headache:	daily _____	sometimes _____	rarely _____	never _____
c) Sleep helps my headache:	daily _____	sometimes _____	rarely _____	never _____
d) Oversleeping produces headache:	daily _____	sometimes _____	rarely _____	never _____
e) I snore:	nightly _____	sometimes _____	rarely _____	never _____
f) After a typical night's sleep, I feel:	refreshed _____	fairly rested _____	somewhat tired _____	very drowsy _____

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\*Reproduced with permission of author [JSP].

### **Sleep diary**

Prospective diaries track the regularity, duration, and quality of sleep. Combined sleep/headache diaries are available to record sleep patterns and other common headache triggers [2]. The diary along with a sleep history is helpful in diagnosing insomnia and circadian rhythm disorders and identifying headache triggers.

### **Polysomnography**

With the possible exception of cluster headache and hypnic headache syndromes, full polysomnography is not routinely indicated in the assessment of headache patients unless a likely sleep disorder is suspected.

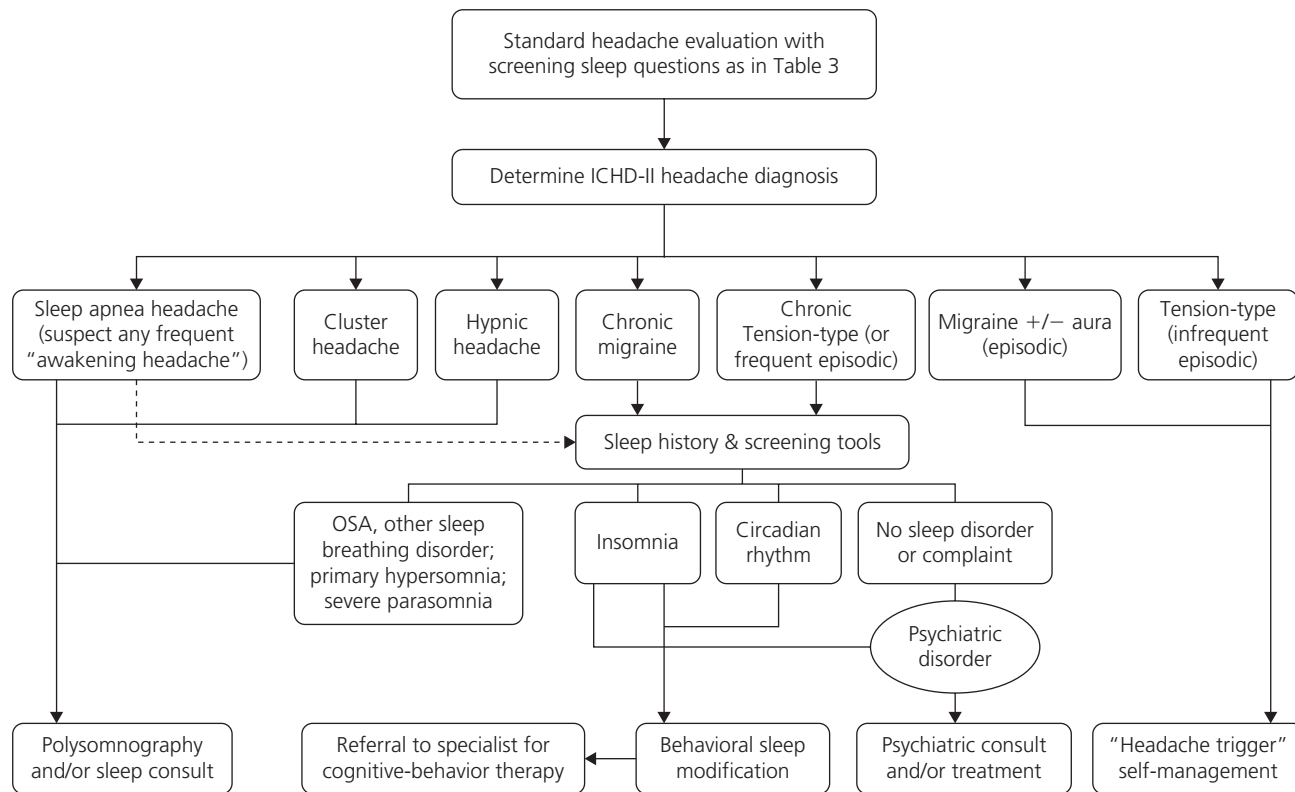
## **Management**

### **Sleep disorders related to headaches**

Clinicians are encouraged to include sleep screening questions with the traditional headache history and diagnose headache according to ICHD-II criteria (figure 14.1). Specific headache diagnoses such as cluster, hypnic, chronic migraine, or tension-type headache with usual onset during or at the termination of sleep (“awakening headache”) may trigger sleep-related investigations. The threshold for polysomnography should be low in both cluster and hypnic headache syndromes.

Patients with chronic migraine and chronic or frequent episodic tension-type headache are at increased risk for insomnia and psychiatric disorders. Particularly those patients refractory to standard treatments (e.g. prophylaxis, withdrawal from medication overuse) should be screened for possible sleep disorders. Episodic headache patients should also be screened when history indicates a specific sleep-related headache trigger or significant sleep-related complaints. Even if sleep complaints are not volunteered, episodic cases may benefit from sleep education regarding headache triggers.

Chronic headache patients treated for sleep apnea with CPAP have improved or resolved headache in one-third to one-half of cases [2,8,23]. Thus, concurrent headache interventions are usually necessary. At this point, variables that predict responders are unknown, so empirical trials in individual patients are justified. Treatment of headache that persists after resolution of sleep apnea or presumably other sleep disorder depends on the exact headache diagnosis, but standard headache therapy recommendations apply. It is prudent to avoid sedation with hypnotics or opiates until the breathing is treated adequately, but after treatment, sedating medications can be considered.



**Figure 14.1** Suggested diagnostic and treatment algorithm for sleep-related headache.

### **Behavioral sleep modification**

Behavioral sleep regulation has been shown to improve chronic migraine and is recommended for chronic headache (migraine and tension-type). Calhoun et al. randomized 43 women with transformed migraine to either a behavioral sleep intervention or sham control group [24]. The sleep group was instructed:

- 1 Schedule consistent bedtime that allows for 8 hours time in bed;
- 2 Eliminate TV, reading, and music in bed;
- 3 Use visualization technique to shorten time to sleep onset;
- 4 Move supper at least 4 hours before bedtime; limit fluids within 2 hours of bedtime; and
- 5 Discontinue naps.

The sham group was instructed to: eat supper at a consistent time, practice acupressure, do 5 minutes of range of motion exercises daily, and eat protein at breakfast.

Both groups received usual medical care. The behavioral sleep intervention yielded a significant reduction in headache frequency and intensity relative to the control group. By the sixth week of treatment, 35% of the treatment group reverted to episodic headache compared to none of the controls. Notably, the improvement in headache was proportionate to the number of sleep behaviors changed – that is, degree of adherence. Though preliminary, this randomized controlled trial provides compelling evidence that a relatively brief behavioral sleep intervention delivered in the headache practice setting can improve headache outcome. Patients with irregular sleep schedules, poor sleep habits, and those spending less than 6.5 or more than 8.5 hours in bed should be counseled in sleep modification as in the Calhoun study above, with more extensive insomnia interventions as needed.

### **Insomnia treatment**

Although insomnia is the sleep complaint most often identified in clinical headache populations, there are no systematic treatment studies of insomnia in headache patients. Although the Calhoun study described above observed headache improvement after behavioral sleep modification, insomnia was not diagnosed in the sample and it is unknown if findings would generalize to the insomnia population [24]. While authors of this chapter have observed certain patients for whom headache improves after improving sleep using behavioral treatment or hypnotics, objective evidence is not available. The best available empirical evidence would be derived from parallel literatures in chronic pain that demonstrate insomnia improves with behavioral sleep interventions.

In the absence of empirical guidance, conventional treatment of insomnia with standard behavioral and pharmacological treatments should be

considered on a case by case basis. Behavior patterns interfering with sleep (e.g. alerting behaviors in bed, worry) or diminishing sleep drive (e.g. excessive amounts of time in bed not sleeping, daytime napping) can be addressed in some headache treatment facilities or patients may warrant referral for cognitive behavioral therapy. Antidepressants with sedative properties such as tricyclic antidepressants or anticonvulsants may provide benefit from headache as well as sleep enhancement. Benzodiazepine and non-benzodiazepine hypnotics are available for treatment of insomnia, and their use may be balanced against the risks, including dependency and tolerance, risk of falls, cognitive problems, and other known adverse effects. Some hypnotic agents may be more appropriate for chronic use than others, but intermittent dosing (2 to 5 times per week) is usually desirable.

### **Psychiatric referral or treatment**

Mood and anxiety disorders are comorbid with insomnia as well as migraine and tension-type headache. Discussed elsewhere [1,2], sleep disturbance (increased or decreased sleep) is a diagnostic symptom of a number of psychiatric disorders, and occurs in the majority of patients with depression, anxiety, and chemical dependencies. Considering the full headache-sleep-affective symptom constellation may yield opportunities to maximize treatment. There is little research to direct treatment. However, recognition of insomnia with depression or anxiety may guide headache prophylaxis toward sedating antidepressants or anticonvulsants, while hypersomnia would call for neutral or more alerting medications [2].

### **Conclusions**

At this juncture, there is no empirical evidence that sleep evaluation or treatment should supersede standard headache care. The evidence that sleep and headache mutually influence each other is based on considerable clinical observations, epidemiological data, case-control studies, and proposed common neuro-anatomic pathways. Unfortunately, there are few controlled trials assessing headache outcomes following intervention and management of sleep-related problems. The best data relates to CPAP therapy for sleep apnea headache although there are no placebo-controlled or long-term trials. There is preliminary evidence for behavioral sleep regulation as an effective option for chronic migraine. In advance of evidence-based algorithms, the recommendations are preliminary and unvalidated. As such, identification and management of sleep-related headache should be considered complementary to standard pharmacological and behavioral headache treatments.

**Key points**

- Sleep may relieve certain headache syndromes but provoke others.
- Comorbidity of sleep and headache disorders is common. There appears to be a link both between sleep disorders and nonspecific headache syndromes such as chronic daily or morning headaches and also to more specific headache disorders such as cluster headache or migraine.
- Patients with chronic headache should routinely be screened for sleep disorders, for example, by including a few sleep screening questions in the “traditional” headache history.
- Patients with chronic migraine and chronic or frequent episodic tension-type headache are at increased risk for insomnia and psychiatric disorders.
- Although there is no conclusive empirical evidence that sleep evaluation or treatment should supersede standard management of headache syndromes, treatment of associated sleep problems may be a useful adjunct. The best data relates to CPAP therapy for sleep apnea headache and behavioral sleep regulation for chronic migraine.

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## CHAPTER 15

# Sleep epilepsies

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### Introduction

The close relationship between sleep and epilepsy has been recognized since the time of Hippocrates and Aristotle. Sleep and sleep deprivation, in particular, may trigger clinical seizures as well as increasing interictal epileptiform discharges (IED) in the absence of observable clinical events. As early as 1947 Gibbs and Gibbs [1] first described the potential importance of the sleep state as a means of enhancing or inducing IED in predisposed subjects. They studied 174 patients with generalized seizures and found that 63% had “seizure discharges” during sleep compared with 19% during wakefulness. Other studies showed that sleep activates both focal and generalized IED and that the occurrence of seizures in the sleep state is observed in nearly one-third of young epileptic patients [2].

In 1885, Gowers was the first to classify epileptic patients into three groups based on the distribution of “fits” over the day with diurnal, nocturnal, and diffuse patterns noted. More contemporary studies have also confirmed that seizure occurrence is far from random across the 24-hour period. Specific epilepsy syndromes have a marked tendency to manifest only or predominantly during sleep. This group include nocturnal frontal lobe epilepsy (NFLE), benign epilepsy of childhood with centrotemporal spikes (BECT), juvenile myoclonic epilepsy (JME), continuous spikes waves during non-REM sleep (CSWS), and Landau-Kleffner syndrome (LKS). CSWS and LKS describe the clinical epileptic syndromes seen in association with electrical status epilepticus in sleep (ESES).



## **The influence of sleep stages on seizures**

The precise stage of sleep is known to influence the relative likelihood of IED and nocturnal seizures. In general, non-REM sleep is associated with an increased incidence and spread of IED as well as clinical manifestations of epileptic activity originating from frontal and temporal lobes [3]. Electroclinical events are most frequent in stage 2 non-REM, followed, in order, by stage 1, stage 3, and then stage 4. REM sleep is a relatively “anti-epileptic” state with suppression of IED and both localized or spreading clinical seizure activity. This relative epileptic risk of different sleep stages can be understood in terms of the varying tendency for wave-like oscillations between the stages. The main structure responsible for generating sleep oscillations is the thalamocortical axis that is modulated by the ascending brainstem and basal forebrain inputs [4]. In non-REM sleep, EEG activity is more synchronized, leading to long-lasting oscillations of rhythmical burst-phase firing patterns which, in turn, tend to increase the magnitude and propagation of postsynaptic responses, including epileptic discharges. During REM sleep and alert waking, cortical neurons tend to fire asynchronously. This pattern generates divergent synaptic signals both temporally and spatially, making propagation of epileptic discharges less likely.

It is also possible that the different state-dependency of skeletal muscle tone may contribute to the increased susceptibility to seizure activity during non-REM compared to REM sleep. In particular, the atonia and active inhibition of voluntary muscle tone in REM sleep, in contrast to non-REM sleep, may further reduce the likelihood of observing clinical seizure activity during REM sleep.

## **Clinical epidemiology**

### **Nocturnal frontal lobe epilepsy**

Nocturnal frontal lobe epilepsy (NFLE) is usually an idiopathic partial epilepsy characterized by a wide spectrum of stereotyped motor manifestations, mostly occurring during non-REM sleep. Nocturnal frontal lobe epilepsy appears to be relatively rare but is probably underdiagnosed since semiological similarities with many parasomnias together with nonspecific surface EEG findings can make diagnosis difficult [5]. Nocturnal frontal lobe epilepsy generally starts during infancy or childhood and persists into adulthood.

### **Benign epilepsy of childhood with centrotemporal spikes**

Benign epilepsy of childhood with centrotemporal spikes (BECT) is the most common epileptic syndrome in childhood [6]. Its prevalence among

early schoolchildren with epilepsy is 23–24% with an age at onset ranging between 2 and 13 years (mean 7 years). The seizures occur during sleep in approximately 75% of the affected children and are characterized by hemifacial motor seizures, often preceded by somatosensory symptoms involving the inner cheek, tongue, and lips.

### **Juvenile myoclonic epilepsy**

Juvenile myoclonic epilepsy (JME) is a common idiopathic generalized and age-related epileptic syndrome which occurs in 5–11% of all epileptic subjects [7] and may have a familial basis. Juvenile myoclonic epilepsy usually starts in puberty or late childhood and is characterized by frequent myoclonic jerks, mainly on morning awakening or soon after. A slight female preponderance has been reported in several studies. A diagnosis of JME can be missed relatively easily and between 25% and 90% of patients referred to neurology or epilepsy clinics are initially misdiagnosed. Contributory factors include failure to elicit a history of myoclonic jerks, misinterpretation of myoclonic jerks as simple partial seizures (especially if unilateral), and general lack of familiarity with the syndrome by nonspecialists.

### **Continuous spikes waves during non-REM sleep/Landau-Kleffner syndrome**

The exact incidence of continuous spikes waves during non-REM sleep (CSWS) and Landau-Kleffner syndrome (LKS) is unknown [8]. These epilepsies appear to be rare but, again, are probably under-recognized conditions. In the medical literature to date, 44 convincing cases of CSWS have been reported whereas approximately 200 cases of LKS were described between 1968 and 1992. In a review of 1497 overnight video-EEG monitoring studies conducted in children over a 5-year interval, Van Hirtum-Das et al. [9] found 18 (1.2%) cases which met the criteria for LKS.

## **Signs and symptoms**

### **Nocturnal frontal lobe epilepsy**

Nocturnal frontal lobe epilepsy is characterized by repetitive episodes of predominantly motor phenomena which recur through the night and occur several nights per week. Events are highly stereotyped, usually starting in childhood with persistence into young adulthood [5]. Since 1985, a familial clustering of NFLE was apparent from several reports. In 1994 and 1995, Scheffer et al. [10] reported five families with NFLE inherited as an autosomal dominant trait and introduced the term of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Overall, a family history of possible nocturnal frontal lobe seizures is found in about 25% of all NFLE cases.

Three subtypes of attacks may be observed both in NFLE/ADNFLE:

- 1 paroxysmal arousals (PA) with short sudden motor attacks or stereotyped behaviors;
- 2 episodes with complex dystonic-dyskinetic components (formerly known as nocturnal paroxysmal dystonia or NPD);
- 3 episodic complex attacks consisting of agitation with mobilization or epileptic nocturnal wanderings (ENW).

Paroxysmal arousals consist of brief (< 20 s), sudden and often very frequent arousals associated with apparently purposeful or semipurposeful behavior. There may be an element of stereotypy to the events. Abrupt elevations of the head, neck, or sometimes trunk from the bed with screaming, moaning, or a fearful expression are common manifestations. Dystonic arm or leg movements are frequent, as is facial grimacing and chewing.

Nocturnal paroxysmal dystonia episodes (duration 30–100 s) sometimes start as paroxysmal arousals but usually progress to produce more complex motor behaviors with prominent dystonic-dyskinetic components such as asymmetric posturing, cycling and kicking of the legs, repetitive and rhythmic limb movements, pelvis or body rocking. The movements may be accompanied by guttural sounds or vocalizations with fearful facial expressions. The stereotypical nature of the episodes for individual subjects remains a highly characteristic feature.

Epileptic nocturnal wandering is a relatively rare phenomenon characterized by prolonged episodes (1 to 3 minutes) with general agitation, sudden standing and ambulation, often mimicking sleepwalking episodes.

Neurological examination in NFLE is generally normal and affected individuals are typically of normal intelligence. Rarely, families with ADNFLE have been reported to exhibit intellectual disability and/or psychiatric disorders such as depression, personality disorder, or paranoid schizophrenia.

### **Benign epilepsy of childhood with centrottemporal spikes**

Benign epilepsy of childhood with centrottemporal spikes is an idiopathic age-specific epileptic syndrome with a high genetic predisposition and a benign course. In BECT, seizures are typically unilateral focal motor (clonic) attacks involving the face, arm, and rarely the leg. Secondary tonic-clonic or generalized fits are frequent and affect 20–50% of subjects. The seizures may have a sensory component, provoking speech impairment or a sensation of dysphagia and even suffocation. Guttural noises arising from involvement of pharyngeal and laryngeal muscles are common. Events usually appear at sleep-wake transitions and tend to be grouped in clusters with prolonged seizure-free intervals [11]. In children younger than 5 years around 15% have only generalized seizures, most of which are nocturnal.

### **Juvenile myoclonic epilepsy**

Juvenile myoclonic epilepsy usually starts in puberty or late infancy and is classically characterized by three semiological features:

- 1 early morning myoclonic jerks involving the upper limbs;
- 2 brief interruption of consciousness or awareness;
- 3 generalized tonic-clonic seizures (GTCS).

About 20% of patients experience all three types of seizures, while 75% of patients suffer both myoclonic jerks and GTCS [12]. In rare cases, an early onset with typical absences followed many years later by myoclonic jerks may be observed and this may represent a diagnostic dilemma. However, absence seizures in JME are mild and often subclinical, in contrast to typical generalized absence seizures of childhood.

Juvenile myoclonic epilepsy seizures are typical during sleep, in the transition from sleep to awakening or upon awakening. However, an atypical circadian distribution may be observed in about one-third of patients with some subjects complaining of myoclonic jerks during the whole day, some of purely diurnal GTCS, and some of nocturnal GTCS. Juvenile myoclonic epilepsy is associated with normal intelligence and clinical neurological examination.

### **Continuous spikes waves during non-REM sleep**

The age of CSWS onset is variable, ranging from 1 to 14 years (usually between 4 and 8 years). Children with CSWS often present with global regression. A range of deficits is observed including loss of language and temporospatial skills, short-term memory deficits, poor reasoning, hyperactivity, and aggressiveness [8]. Regarding language impairment, an expressive aphasia is typical with comprehension generally spared. There are also motor deficits, resulting in ataxia, dystonia, and dyspraxia, which may be predominantly unilateral.

In 80% of patients with CSWS, seizures are the presenting symptom. Most children experience multiple seizures per day. The seizure types are very varied and include generalized tonic-clonic events, typical absence, atypical absence, simple and complex partial seizures. Despite the EEG abnormalities during sleep in these patients, the sleep pattern may appear surprisingly normal.

### **Landau-Kleffner syndrome**

The age of onset of LKS ranges from 3 to 8 years with a peak at 4 to 5 years. The primary clinical manifestation is language regression: an acquired auditory agnosia may progress over weeks to months [8]. Affected children may be unable to understand spoken language or appear deaf. Other possible clinical symptoms are hyperkinesia, irritability, attention deficit disorder,

and autistic-like behavior. Before the onset of LKS, language and behavior in the majority of the children appear unremarkable and milestones are generally normal. Seizures in LKS are relatively infrequent but include generalized clonic, partial clonic, and atypical absence attacks.

There is an overlap between CSWS and LKS, but children with CSWS present with more global symptoms of regression and have more problematic epilepsy. In both, there may be little in the way of sleep symptomology despite the EEG abnormalities during sleep.

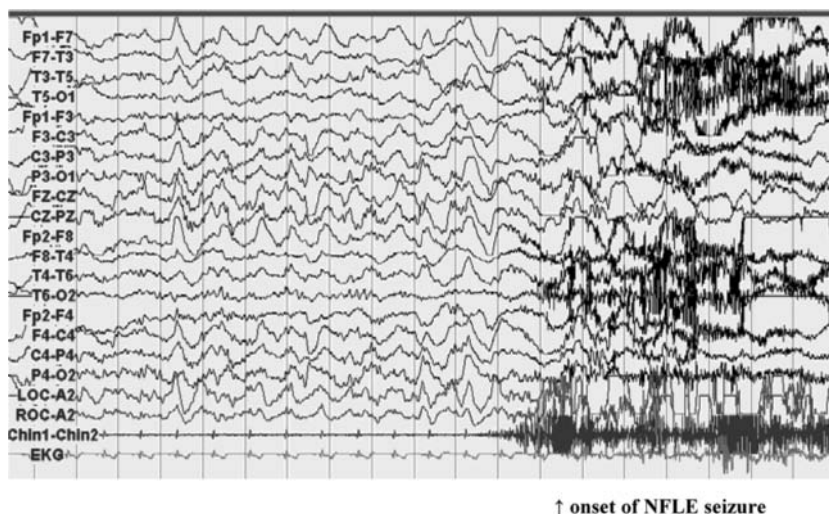
## Diagnostic procedures

### Nocturnal frontal lobe epilepsy

In NFLE, nocturnal video-polysomnography is now considered the gold standard for confident diagnosis. Most seizures appear during non-REM sleep with a preponderance in stage 2 non-REM (> 60%). In some cases, the motor attacks (especially PA) show a clear periodicity (every 20 seconds to 2 minutes). A recent study showed, however, that the interobserver reliability of NFLE diagnosis, based on videotaped observation of sleep motor phenomena, is not always satisfactory [13].

Due to the presence of significant movement artefact from muscle, EEG during episodes is uninformative in almost half of cases. However, rhythmic theta or delta waves, sharp waves predominantly in the frontal regions, attenuation of the background activity, and, in a minority of cases, classic spike-and-wave activity or small amplitude fast activity may be recorded during ictal or interictal EEGs. A burst of delta activity may also frequently precede or be simultaneous with the episode. Arousal fluctuations, expressed with periodic delta bursts, do not readily discriminate epileptic subjects from those with non-REM parasomnias (confusional arousals, sleep terrors, or sleepwalking) as they are relatively common in both [14]. This emphasizes the utility of video-recording along with polysomnography (figure 15.1).

It has been postulated that the complexity of the motor behavior in NFLE reflects a unique mechanism of propagation of electrical discharges within the frontal lobe. Some authors have confirmed this hypothesis in NFLE patients using intracerebral recording techniques, particularly in seizures starting within the supplementary motor area [15]. Such deep electrode recordings have also demonstrated that seizures assumed to arise from orbitofrontal zones may actually originate in temporal lobe areas, especially if affective symptomology and agitation are prominent as with ambulatory behaviors seen in ENW. Such seizures probably involve large neuronal networks that emerge from frontal areas (orbitofrontal and anterior cingulate) with spreading to temporal limbic cortices. Autonomic



**Figure 15.1** 20-second EEG epoch, showing the onset of a NFLE seizure.

changes such as tachycardia, tachypnea or respiratory abnormalities, and electrodermal changes, are frequently observed during the attacks.

Neuro-imaging studies (CT, MRI) are generally normal in NFLE patients but should be performed, largely to exclude developmental lesions such as dysplasia or heterotopia. Some sophisticated genetic and neuro-imaging techniques have been used for evaluating NFLE/ADNFLE but clinical applications are very limited. In particular, a mutation of the neural nicotinic acetylcholine receptor (nAChR) alpha-4 subunit has been found in individuals with ADNFLE, with further studies demonstrating other mutations within the nAChR system [16]. A recent PET study in patients with ADNFLE showed a reduction of the nicotinic receptors in the prefrontal cortex and an increase of these receptors in the brainstem [17]. Interestingly, the nAChR is known to exert a modulating effect on sleep and arousal oscillations at both cortical and subcortical levels.

Although nocturnal video-polysomnography is recommended in most patients, it remains an expensive procedure and is not universally available. A new scale, the Frontal Lobe Epilepsy and Parasomnia (FLEP) scale, was recently proposed as a tool for distinguishing NFLE from parasomnias, especially non-REM arousal parasomnias such as sleepwalking and night terrors [18]. In the FLEP scale, responses favoring epilepsy score positively and those favoring parasomnias score negatively (table 15.1). Although controversial, it is possible that the FLEP scale may allow a confident diagnosis in many patients without the need for video-polysomnography [19]. For further details on the distinction between seizures and parasomnias, see chapter 16.

**Table 15.1** The frontal lobe epilepsy and parasomnias (FLEP) scale [18]

Clinical feature		Score
Age at onset		
At what age did the patient have their first clinical event?	< 55 y	0
	≥ 55y	−1
Duration		
What is the duration of a typical event?	< 2 min	+1
	2–10 min	0
	> 10 min	−2
Clustering		
What is the typical number of events to occur in a single night?	1 or 2	0
	3–5	+1
	>5	+2
Timing		
At what time of night do the events most commonly occur?	Within 30 min of sleep onset	+1
	Other times (including if no clear pattern identified)	0
Symptoms		
Are the events associated with a definite aura?	Yes	+2
	No	0
Does the patient ever wander outside the bedroom during the events?	Yes	−2
	No (or uncertain)	0
Does the patient perform complex, directed behaviors (e.g. picking up objects, dressing) during events?	Yes	−2
	No (or uncertain)	0
Is there a clear history of prominent dystonic posturing, tonic limb extension, or cramping during events?	Yes	+1
	No (or uncertain)	0
Sterotypy		
Are the events highly stereotyped or variable in nature?	Highly stereotyped	+1
	Some variability/uncertain	0
	Highly variable	−1
Recall		
Does the patient recall the events?	Yes, lucid recall	+1
	No, or vague recollection only	0
Vocalization		
Does the patient speak during the events and, if so, is there subsequent recollection of this speech?	No	0
	Yes, sounds only or single words	0
	Yes, coherent speech with incomplete or no recall	−2
	Yes, coherent speech with recall	+2
Total score		

### **Benign epilepsy of childhood with centrotemporal spikes**

The EEG pattern in BECT is quite specific. Epileptiform foci are seen in the presence of a normal background activity. The activation of epileptic discharges is observed during non-REM sleep with a typical morphology consisting of biphasic or triphasic sharp waves of relatively high amplitude, localized in centrotemporal regions. The electrical field may also include the contralateral homolog zone. The spikes may variably appear as independent or bilateral in the same or different records.

### **Juvenile myoclonic epilepsy**

In JME, the clinical diagnosis is supported by compatible EEG changes showing generalized polyspike-and-wave patterns without background slow waves in the presence of normal brain imaging and clinical neurological examination. However, relying solely on the EEG to diagnose JME can be troublesome. Indeed, several studies have suggested that even serial EEGs do not reveal the suggestive abnormalities of generalized epilepsy in 21–54% of patients [12]. In patients with normal EEGs or with focal/lateralized epileptiform discharges, a video-EEG monitoring for 1 or 2 days may be required to make a correct diagnosis of JME [12].

Some studies have implied that JME patients have a personality profile characterized by immaturity, irresponsibility, emotional instability, and indifference to their disease. This is controversial especially in the light of a recent prospective study that enrolled patients before drug treatment and found no convincing personality traits [20].

### **Electrical status epilepticus in sleep**

An EEG during sleep is clearly required to make a diagnosis of ESES. In non-REM sleep, the epileptiform discharges are highly activated and become continuous or nearly so. Overall, the sleep structure appears normal, but the presence of almost continuous spike-wave discharges makes the recognition of normal sleep EEG elements, such as K-complexes, spindles, or vertex sharp transients, quite difficult. Although the epileptiform discharges have been described as generalized, they arise focally and are then rapidly propagated within and between hemispheres.

Maximal spike location varies between CSWS and LKS. In CSWS, the wake EEG shows focal, multifocal, or diffuse discharges, often with frontotemporal or frontocentral predominance [8]. In LKS, the EEG during wakefulness is variable and may show focal, multifocal, or generalized epileptic abnormalities or even be normal. The focal epileptiform activity in LKS is usually posterotemporal.



A subgroup of children with ESES may have significantly less activation of epileptiform discharges in stages 1 and 2 non-REM compared to slow-wave sleep and a full overnight recording should be considered in some cases.

Neuropsychological tests in ESES patients are important to determine the type and extent of cognitive impairment. Some centers advocate PET and SPECT studies to correlate neuropsychological dysfunction with altered metabolism in frontotemporal or posterotemporal areas.

Magnetic resonance imaging should be considered in children with CSWS as abnormalities including cortical dysplasia, congenital stroke, diffuse atrophy, white-matter changes, abnormal or delayed myelination have been described in CSWS. Patients with LKS, by contrast, generally have normal imaging.

## Management

### Nocturnal frontal lobe epilepsy

Nocturnal frontal lobe epilepsy is considered a relatively benign clinical entity because seizures occur during sleep and most cases respond positively to antiepileptic drugs. Controlled drug trials are lacking but published data suggests about two-thirds of NFLE patients respond well to carbamazepine at low doses (200–600 mg at bedtime), with greatly reduced seizure frequency and complexity.

Of the newer drugs for epilepsy, there is evidence that topiramate (dose range 50–300 mg at bedtime) can be effective in NFLE. The agent was evaluated in 24 patients with a mean age of 29 years. Seizure freedom was achieved in 25% and seizure reduction by 50% in 62.5%. Weight loss was observed in six cases and speech dysfunction in two [21]. Oxcarbazepine (dose range 15–45 mg/kg/day) in eight children aged between 4 and 16 years was reportedly extremely effective in all cases with mild side effects of transient diplopia in one case and somnolence in another [22]. One case report has tried a transdermal nicotine patch with success [23]. This positive effect could be related to possible mutations on the nAChRs described in familial NFLE. Of interest, a significant association between tobacco use and seizure control has been observed in a group of ADNFLE patients in contrast to nonsmokers [24].

About 30% of NFLE cases with more frequent and complex attacks in larger samples are resistant to antiepileptic drugs. Surgical treatment may have an indication in these nonresponders who also usually have significant sleep fragmentation, non-restorative sleep, and troublesome daytime sleepiness. An accurate presurgical evaluation, including invasive EEG recording, is mandatory before resective surgery in drug-resistant NFLE is considered.

### **Benign epilepsy of childhood with centrotemporal spikes**

Overall, prognosis in BECT is excellent with a satisfactory response usually observed with most standard antiepileptic drugs. Subsequent remission of symptoms before age 16 should be anticipated in the majority of the patients once antiepileptic drugs are discontinued. A minority (6–18%), unfortunately, have numerous events despite therapeutic trials with several drugs. A poor clinical course with frequent seizures is associated with early onset, often before the age of 3 years.

A worsening of BECT has also been observed as a direct side effect of certain antiepileptic drugs [25]. Indeed, some patients show seizure exacerbation following carbamazepine or oxcarbazepine treatment with progression to atypical absences, neuropsychological disturbances, and even CSWS. Seizure worsening and CSWS have been also reported in a few BECT patients treated with valproate or phenobarbital.

### **Juvenile myoclonic epilepsy**

In JME, many studies have reported that 70–90% of patients show a good response to a variety of standard antiepileptic drugs such as valproate, lamotrigine, topiramate, and levetiracetam. However, spontaneous remission is uncommon and lifelong medical treatment with modification of lifestyle issues is often considered appropriate. Avoidance of binge alcohol drinking and sleep deprivation is strongly recommended.

### **Electrical status epilepticus in sleep**

In ESES, the goal of treatment is not only to control the seizures but also to improve neuropsychological function. With regard to the latter, this provides an incentive to try and normalize EEG abnormalities even if clinical seizures are controlled [8]. Phenytoin, carbamazepine, and barbiturates may reduce the seizures but are probably contraindicated in ESES because they can potentially worsen both the neuropsychological outcome and the neurophysiological abnormalities. Valproate, ethosuximide, levetiracetam, or diazepam have been reported to be beneficial in some small case series. As a rule, polypharmacy should be avoided in ESES. Indeed, one study showed that the reduction of polytherapy coincided with an improvement in the syndrome.

Some authors [26] reported improved speech abnormalities and normalization of the EEG in all of three children with LKS treated with corticosteroids. They suggested that steroids should be given in high doses as soon as the diagnosis is established, followed by maintenance doses for several months to years. Other studies have showed that the earlier steroids are started, the shorter the duration required and the better the outcome. Early tapering of steroid doses may be associated with relapse

of ESES and neuropsychological deterioration, ultimately necessitating a longer treatment duration.

In the absence of clear evidence, other therapies include intravenous gamma-globulin (2 g/kg over 4 days), ketogenic diets, vagal nerve stimulation, and surgical therapy with multiple subpial transection in drug-resistant cases.

Although the epileptic seizures resolve with time in most cases, many children are left with significant cognitive or language impairment. Not surprisingly, longer duration of ESES appears to be the major predictor of poor outcome.

### Key points

- An intimate relation between epilepsy and sleep has long been recognized.
- Specific epilepsy syndromes have a marked tendency to manifest only or predominantly during sleep, particularly non-REM stages.
- Some seizure syndromes manifest predominantly at sleep-wake transitions.
- Many generalized epilepsies are sensitive to sleep deprivation, a fact sometimes helpful in diagnostic procedures.
- Diagnosis of nocturnal seizures may be difficult, and generally requires a combination of careful history, nocturnal video recordings, and nocturnal EEG recordings.
- New scales such as the FLEP scale may increase diagnostic confidence, reducing the need for intensive monitoring.
- Management depends on the specific syndrome diagnosed although controlled evidence-based information is limited.

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## CHAPTER 16

# Seizures versus parasomnias

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### Introduction

It is universally accepted that humans and warm-blooded animals are either awake or in distinct states of REM and non-REM sleep [1]. However, defining the point of transition between these states is somewhat arbitrary and paroxysmal events may arise from the boundary between sleep and wake. In humans, this boundary is often indistinct. For example, on being awoken from stage 1 sleep all the volunteers examined by Dement and Kleitman in 1957 said that they had not yet fallen asleep and reported mental activity full of imaginary content called “hypnagogic rêverie” [2]. This particular behavior is called “*dormiveglia*” in Italian – an untranslatable term combining the Italian words for sleep and wake, and proposed by Kleitman himself [3]. Moreover, a recent taxonomic analysis of the physiological variables of human sleep concluded that stage 1 of human sleep resembles wakefulness and REM sleep rather than synchronized non-REM sleep (defined by spindles and delta sleep) [4]. As initially suggested by McDonald Critchley [5], we think that in practical terms it is appropriate to distinguish the states of sleep onset or pre-dormitum [1] and awakening or post-dormitum [2] from sleep proper which is unequivocally divided into synchronized sleep (spindles and delta sleep) [3] and REM sleep [4]. Sleep-related epileptic and non-epileptic paroxysmal events will be described within this framework and discussed, adopting the terms suggested by the latest international classifications [6,7].

## **Sleep-related epileptic events**

See also chapter 15.

### **Arising at sleep onset (pre-dormitum)**

Focal and diffuse interictal EEG epileptic discharges are often facilitated by drowsiness and the pre-dormitum (stage 1), especially when EEG recordings are performed after sleep deprivation. However, clinical epileptic events seldom arise as the subject falls asleep.

### **Arising at awakening (post-dormitum)**

Two variants of generalized epilepsy are closely linked with awakening: idiopathic generalized epilepsy, characterized by tonic-clonic seizures (TCS), and juvenile myoclonic epilepsy (JME) which is characterized by diffuse myoclonic jerks and a variable frequency of generalised seizure activity.

The TCS and myoclonic jerks characterizing these conditions typically arise after awakening when patients are washing or having breakfast. Sleep deprivation, especially in the context of previous alcohol intake, facilitates both of these epileptic events.

### **Arising during synchronized non-REM sleep**

Synchronized sleep facilitates the onset and diffusion of focal interictal discharges [8]. Focal seizures may occur mainly or exclusively during synchronized sleep with occasional secondary generalization (nocturnal TCS). Lennox-Gastaut syndrome and other “malignant” or atypical variants of generalized epilepsy often feature nocturnal tonic attacks of which patients and their relatives could be unaware.

### **Benign childhood epilepsy with centrotemporal spikes**

Benign childhood epilepsy with centrotemporal spikes (BECT) is a partial epilepsy typically arising in children between 4 and 8 years of age and ceasing as a rule by the age of 14 [9]. The children present with hemiconvulsive seizures during synchronized sleep, often involving the orofacial region. There is often an associated characteristic rhythmical noise which typically alerts parents to the seizure. This is followed by aphasia for several seconds. Nocturnal BECT seizures usually recur after months or even years and typically cease a few years after onset in favorable cases.

### **Nocturnal frontal lobe epilepsy**

Seizures occurring in this form of epilepsy are strictly linked to synchronized non-REM sleep. Nocturnal frontal lobe epilepsy (NFLE) is probably relatively common but was only identified in the 1970s when polysomnographic

recordings started to be routinely performed under audiovisual control. Prior to that, NFLE was often confused with arousal disorders (see below).

### **Paroxysmal arousals**

Paroxysmal arousal (PA) events consist of apparent sudden awakenings associated with stereotyped movements (such as suddenly sitting up in bed, grabbing the pillow, or kneeling on the bed). Patients stare wide-eyed and almost always exhibit dystonic postures of a hand and arm and/or dyskinetic movements (choreo-athetotic or ballistic) of a limb, typically the arm. Attacks are frequent and highly stereotyped, recurring nightly with many times each night.

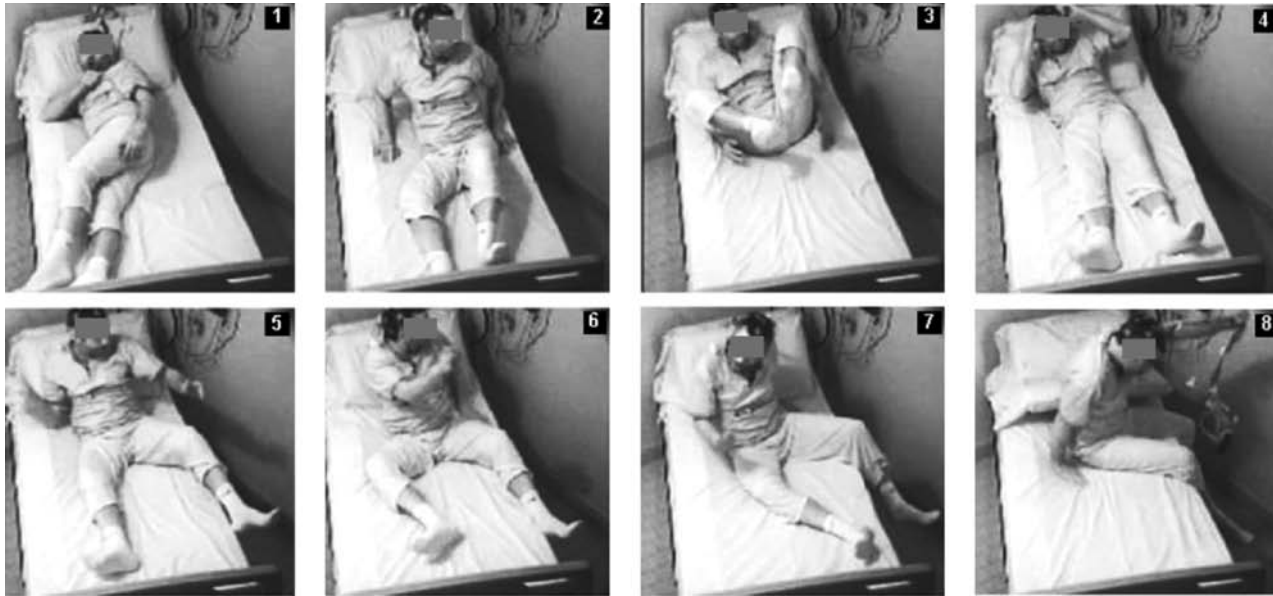
### **Nocturnal paroxysmal dystonia**

The seizures in nocturnal paroxysmal dystonia (NPD) last longer (30–50 seconds). Like paroxysmal arousals, they start with a sudden apparent awakening but then develop into a more complex motor behavior. If the dystonic component prevails, attacks resemble supplementary motor area seizures characterized by head deviation to one side, extension of the ipsilateral limbs and flexion of the contralateral limbs. If the dyskinetic component prevails, seizures may be characterized by choreatic movements with violent torsion of the trunk and limbs which may fling in all directions. Alternatively, rhythmic trunk movements (repeated flexion-extension movements of the trunk on the pelvis), rocking (coital-like) movements of the pelvis, or repeated hand or foot movements may predominate. In addition, patients may emit guttural sounds, curse, or swear. They may even whistle, spit, or appear supplicant (see figure 16.1). These behavioral disorders are accompanied by major autonomic changes in breathing, heart rate and electrodermographic activity. Nocturnal paroxysmal dystonia is commonly associated with paroxysmal arousal. On awakening after symptomatic nights, patients may feel exhausted with a sense of having slept badly.

### **Episodic (epileptic) nocturnal wandering**

Episodic (epileptic) nocturnal wandering (ENW) is much less common than the other NFLE seizure types, recurring, as a rule, after weeks, months or even years. The onset of ENW is similar to that of PA and NPD but patients subsequently get out of bed and start jumping or hopping about the room, often resembling a crude marionette. An episode of ENW can last several minutes. The patients we have examined invariably experienced numerous minor events (PAs and NPD) that were also recorded on the nights when ENW did not occur.

In exceptional cases, NPD and ENW attacks may develop into generalized seizures and very rarely arise from apparent wakefulness. NFLE tend to start in early childhood but cases of adult onset have been reported.



**Figure 16.1** Nocturnal paroxysmal dystonia (NPD) seizure with a photographic sequence of eight images taken at 3-second intervals. The patient turns his head to the left (1), suddenly sits up in bed (2), raises his legs and rocks his pelvis (3). He then he lies down on the bed again, raising his hands to his head (4), opening his legs and arms (5), and making repetitive head movements with vocalizations tongue movements (6,7). Finally he sits up in bed and grabs hold of the montage leads (8).



**Arising from REM sleep**

Focal interictal abnormalities tend to not to propagate and disappear in REM sleep. Clinically ictal episodes seldom arise from REM sleep.

**Sleep-related non-epileptic paroxysmal events**

See table 16.1.

**Arising around sleep onset (pre-dormitum)**

A variety of brief motor phenomena may arise in the boundary between wake and sleep proper, the so-called pre-dormitum.

**Sleep starts or hypnic jerks**

These consist of sudden and brief contractions largely of axial muscles involving one or more body segments such as the neck, trunk, and occasionally a proximal limb. The body jerks are dramatic and may be accompanied by a feeling of falling into a void. There may be associated sensory phenomena such as flashes or loud bangs and, less frequently,

**Table 16.1** Classification of non-epileptic events related to sleep stage

At sleep onset (pre-dormitum)	Sleep starts Nocturnal myoclonus (periodic limb movements) when associated with RLS Propriospinal myoclonus at sleep onset Hypnagogic hallucinations Central breathing arrests
During synchronized NREM sleep (usually in the first third of the night)	Confusional arousals Sleep terrors Sleepwalking Nocturnal myoclonus (periodic limb movements)
During REM sleep (usually in the second part of the night)	Nightmares REM sleep behavior disorders (RBD) Sleep paralysis
At morning awakening (post-dormitum)	Sleep drunkenness Hypnopompic hallucinations
Various times of the night	Sleep enuresis Benign sleep myoclonus of infancy Sleep bruxism Nocturnal faciomandibular myoclonus Rhythmic movement disorder Sleep-related groaning (catathrenia)

formed hallucinations. Sleep starts recur sporadically and are almost universal at a mild level, described by more than 80% of people [7]. They are more common in children than in adults and should be considered physiological.

### **Periodic limb movements or nocturnal myoclonus**

These consist of relatively slow clonic, polyclonic, or tonic-clonic muscle contractions lasting between 0.5 and 2 seconds, recurring in periodic sequences roughly every 20–40 seconds. The phenotype, intensity, and frequency of periodic limb movements vary widely although the jerks involve the distal portions of the legs predominantly. The propagation of the movements also varies, consisting of only big toe extension or developing into a triple flexion of a limb with subsequent foot dorsiflexion and knee flexion (see figure 16.2) [10]. Periodic limb movements are almost always bilateral and synchronous but asymmetric. Sometimes the movements alternate from one side to the other. Periodic limb movements may sometimes be viewed as a physiological event, appearing during light sleep (stage 2) and without the intensity or duration to disturb sleep significantly [11]. They may occur in children but are especially prevalent in the elderly. Indeed, they are seen in up to 34% of people over the age of 60 years [7]. The association with restless legs syndrome is described in chapter 8.

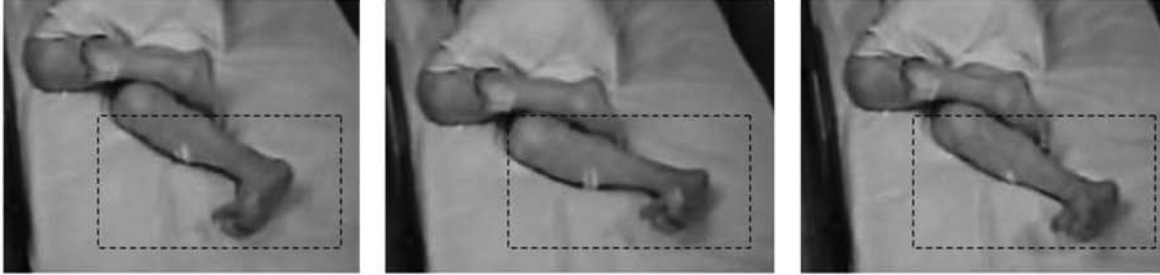
### **Propriospinal myoclonus**

Propriospinal myoclonus (PSM) consists of sudden and often violent jerks initially arising from an axial muscle muscle group (neck, thorax, or abdomen) with subsequent spread up and down intrinsic cord multisynaptic pathways to the whole trunk and all four limbs (see figure 16.2B). Brown and co-workers were the first to describe PSM, noting that the condition is favored by postural rest [12]. In several of our patients, however, PSM was confined specifically to the pre-dormitum, causing severe and resistant sleep onset insomnia. In our cases, PSM was seen to discontinue only with the onset of sleep spindles (i.e. on entering stage 2 non-REM sleep). Exceptionally, PSM may reappear with nocturnal awakenings or in the post-dormitum [13].

### **Hypnagogic and hypnopompic hallucinations**

These are “hallucinatory experiences, principally visual, that occur at sleep onset or on awakening from sleep” [7]. They are fairly common in children (with a prevalence of 25–37%) but are seldom encountered in adults outside the narcoleptic population. A similar phenomenon may occur in those with serious visual impairment due to retinopathy, for example. This can lead to persistent or disturbing hallucinations and severe sleep-onset insomnia. Hallucinatory events similar to those on falling asleep may also appear on awakening (hypnopompic hallucinations).

(A)



(B)



**Figure 16.2** A. Photographic sequence of periodic limb movements: extension of the big toe, dorsal flexion of the foot and right leg. B. Photographic sequence of propriospinal myoclonus: the contraction begins in the paraspinal muscles, spreading to the chest muscles and proximal limb muscles causing them to extend and abduct, raising the body.

### **Central breathing arrests**

The tendency towards periodic breathing on falling asleep may trigger the onset of sporadic central apneas. Sporadic central apneas at sleep onset can be deemed physiological but, under certain circumstances, central apneas lasting 10 to 15 seconds will recur and prevent sleep onset [14]. This is extremely rare in healthy persons living at normal altitude but it is fairly common in climbers, for example, temporarily living in high mountain areas above 3500 m.

### **Arising on awakening (post-dormitum)**

#### **Sleep drunkenness**

This refers to a confused and amnesic state which persists for several minutes or even hours, generally in those suddenly awoken from deep sleep. Significant events are fairly rare and sporadic, occurring mainly in adolescents but also in adults under stress with chronic sleep deprivation. A similar disorder may occasionally arise in patients with obstructive sleep apnea syndrome (OSAS). Sleep drunkenness can be considered as a variant of a “confusional arousal” (see below).

### **Arising from synchronized non-REM sleep**

Most of the non-epileptic paroxysmal events arising in synchronized sleep are also called “arousal disorders” [15]. Arousal disorders can be defined as partial awakenings from deep non-REM sleep [7]. Arousal disorders have been arbitrarily divided into three types depending on the complexity of their features: (1) confusional arousals; (2) sleep terrors; (3) sleepwalking.

#### **Confusional arousals**

These are partial awakenings in which the state of consciousness remains impaired for several minutes without any accompanying major behavioral disorders or severe autonomic responses. Extremely common in childhood (affecting up to 20% of children under 5 years of age), these arousals do not disturb the child’s sleep or usually give cause for parental alarm. They lack any clinical significance and can be often be reproduced artificially by awakening a child from deep sleep.

#### **Sleep terrors**

These are sudden awakenings associated with behavioral and strong autonomic responses. Subjects wriggle or struggle, sit up in bed, cry out or utter incomprehensible words. The children have a terrified expression but cannot respond to family members trying to console them. They are generally pale with signs of sympathetic activation such as tachypnea, tachycardia, mydriatic pupils, and profuse sweating. After a few minutes they calm down spontaneously and return to sleep. If subsequently

awakened, the child usually recalls nothing or gives a vague and confused account of what has happened. Sleep terrors are mainly a childhood phenomenon: their prevalence has been estimated at 1–7% of children, with a peak prevalence at 5–7 years of age and a tendency for spontaneously resolution during adolescence [7].

### **Sleepwalking**

An episode of sleepwalking generally starts as a series of complex behaviors such as changing body position, turning to one side or playing with sheets, sitting up, or kneeling on the bed. The subject then gets up and walks around in a state of altered consciousness and impaired judgment. Typically, the events are calm and simply consist of walking round or out of the bedroom, conducting purposeful or semi-purposeful tasks such as moving objects, talking, or dressing (see figure 16.3). Episodes may vary in duration from 3 to 15 minutes. At the end of the episode, the subject will usually return to his own or the parent's bed and resume sleep. Subsequent recollection is poor. The exact prevalence of sleepwalking is uncertain as it is not commonly reported to doctors. Literature reports vary widely and cite prevalence rates in children from 1% to 15% [16]. Sleepwalking peaks by age 8–12 years with spontaneous termination of episodes by late adolescence in the majority.

Arousal disorder typically occur during the first part of the night when deep non-REM sleep is more intense. Recognized triggers are sleep deprivation or disruption, febrile illness, sleep-related breathing disorders, hypnotics, and alcoholic beverages.

### **Arising from REM sleep**

#### **Nightmares**

Nightmares are “sudden arousals” triggered by a frightening dream of which precise details are recalled. Unlike typical dreams, the memory for the episode remains for a considerable period and similar events may recur on different nights. Nightmares are clearly common in childhood with a prevalence of 5–30%, peaking at ages 3–6 years [16]. In adults they may appear following terrifying experiences with high emotional impact, such as in the victims of road accidents, air crashes, terrorist acts, or natural disasters including earthquakes or storms. “Post-traumatic” nightmares may recur in adults for weeks, months or even years [7].

#### **REM sleep behavior disorder**

REM sleep behavior disorder (RBD) is characterized by a history of apparent dream-enacted behavior consistently associated with a vivid dream mentation. REM sleep behavior disorder arises from REM sleep episodes without atonia [7]. During RBD patients display complex and often violent gestures. Animated or threatening discussions, moaning, punching



**Figure 16.3** A photographic sequence of a typical sleepwalking episode from a home video. The patient opens his eyes (1), sits up in bed (2), moves the sheets (3), and gets up (4), walking towards the desk at the side of the bed. He looks at the computer on the desk for a few seconds (5), then turns round (6), gets back into bed (7), and goes back to sleep (8).

and screaming, are all typical attack or defence reactions. Rarely patients will jump out of bed, continuing to vocalize, curse, or threaten an imaginary aggressor. Positive emotions are also reported and noisy laughs with apparent enjoyment may occasionally be seen. If awakened, patients recount the details of the dream story which tallies with the behavior noted during the episode.

REM sleep behavior disorder is usually more obvious in the second half of the night when REM sleep episodes tend to last longer. Sometimes they recur every night, occurring many times on the same night, lasting from a few minutes to half an hour. Chronic forms, the commonest and most characteristic, prevail in men (male/female ratio 8 : 1) and arise relatively late in life with a mean age at diagnosis of 60 years [17]. The link with neurodegenerative diseases, especially parkinsonian disorders, is discussed in chapter 9.

### **Sleep paralysis**

Sleep paralysis is an inability to perform voluntary movements around sleep-wake transition with episodes lasting from a few seconds to several minutes. The sensation of being paralysed and unable to take voluntary breaths usually gives rise to intense anxiety. Sleep paralysis is associated with narcolepsy, particularly at sleep onset, but also occurs as an isolated sporadic phenomenon. It may occasionally affect 15–40% of the population, especially those under 30 years of age [7] with a positive family history.

## **Other sleep-related non-epileptic paroxysmal events**

### **Sleep enuresis**

Nocturnal episodes of enuresis are only considered abnormal after 5 years of age. Enuresis is classified as primary if episodes recur without long intervals (at least 6 months) after 5 years of age, and secondary if they reappear after that age with an interval of at least 6 months [7]. Primary, often familial, enuresis is usually ascribed to a delayed maturation of physiological control of urination during sleep, whereas secondary enuresis is commonly attributed to psychological factors such as a poor mother–child relationship or family conflict. The evidence to support this association is slim, however.

### **Benign sleep myoclonus of infancy**

Benign sleep myoclonus of infancy (BSMI) consists of repetitive rhythmic or arrhythmic widespread myoclonic jerks and is strictly related to the first 6 months of life. Benign sleep myoclonus of infancy is reportedly rare [7] and occurs in healthy newborn in clusters of 20 to 30 seconds only during sleep. Benign sleep myoclonus of infancy abruptly disappears when the infant is aroused.

**Sleep bruxism**

Bruxism (teeth grinding) is common, often arising in children (between 3 and 12 years). There is no sex prevalence and it tends to recur in families [7]. Bruxism may start as the subject is falling asleep but may persist throughout all sleep stages. If long-lasting, sleep bruxism may cause serious damage to the teeth and gums.

**Nocturnal faciomandibular myoclonus**

Nocturnal faciomandibular myoclonus (NFMM) is a rare sleep-related motor disorder consisting of recurrent and quasi-rhythmic myoclonic jerks involving the masseter, orbicularis oculi, and oris muscles. Violent repeated contractions of the masseter muscles generate a characteristic sound of teeth, likened to a “hollow” recurring bite. It may lead to painful cuts and injuries to the lips, tongue, and oral mucosa, thereby disturbing sleep. NFMM may recur in clusters of several seconds many times a night. It is seen in all sleep stages and often in several family members. Prevalence figures are not known [18].

**Sleep-related rhythmic movement disorders**

Rhythmic movement disorders (RMD) include head banging (*jactatio capitis nocturna*) and body rocking. These are repetitive, stereotyped, and rhythmic motor behaviors generally lasting 5 to 15 seconds with onset during drowsiness but also persisting during sleep, occasionally even confined to the REM stage [19]. Sleep-related RMD arise in normal children and tend to disappear with age. Some claim that RMD are more common and persistent in children with a developmental delay although this remains controversial.

**Sleep-related groaning (catathrenia)**

This is a recently described unusual nocturnal phenomenon consisting of long-lasting expiratory groaning noises, occurring almost every night, mainly in the second half, often during REM stages [20]. The noise occurs without any obvious respiratory distress and is rarely a problem to the subject, in contrast to the bed partner who is invariably alarmed and disturbed by the prolonged groans. Nocturnal groaning has hitherto been described only in adolescents and young adults of both sexes. It has a chronic course. As this event has never been described in the elderly, it may well be that sleep-related nocturnal groaning tends to disappear spontaneously with age.

**Treatment of non-epileptic paroxysmal events**

See also chapter 5.

An approach to treatment is given in table 16.2. It should be recognized that very little controlled evidence exists for these disorders and, where



**Table 16.2** Treatment of sleep-related non-epileptic events

Disorder	Treatment
Sleep starts	Usually only reassurance required. They are a universal component of physiological sleep
Periodic leg movements or nocturnal myoclonus	No medication is required if sleep undisturbed If sleep disturbed: dopaminergic drugs, benzodiazepines, gabapentin are used, often in combination
Propriospinal myoclonus at sleep onset	Clonazepam (0.5–2 mg) at bedtime Opiates may also be effective but carry the risk of dependence
Hypnagogic hallucinations	Usually therapy is unnecessary. If severe, tricyclic antidepressants can help
Sleep paralysis	Reassurance and education usually suffice If frequent: SSRIs or tricyclics
Disorders of arousal	Parental education as to the benign nature of the phenomenon Regular and adequate sleep routine in a safe sleep environment recommended.
Sleep enuresis	Noninvasive approach after identification of causative factors (drinking and voiding chart; alarms if reduced bladder capacity) In individual cases, desmopressin may help
Nightmares	If sporadic: reassurance If chronic or post-traumatic: relaxation therapy or hypnotherapy
REM sleep behavior disorder	Clonazepam (0.5–2 mg) at bedtime Melatonin as second-line alternative (2–6 mg)
Benign sleep myoclonus of infancy	No medication required
Nocturnal faciomandibular myoclonus	Clonazepam (0.5–2 mg) at bedtime
Sleep bruxism	Each subject should be evaluated by a dental practitioner. Pharmacological (benzodiazepines, muscle relaxant) or psychobehavioral (relaxation, biofeedback, training programs, hypnosis) therapies have been described
Sleep-related rhythmic movement disorders	Treatment is usually unnecessary Ensure that children are safe and protected from injury In severe forms: clonazepam at low doses
Sleep-related groaning (catathrenia)	Unknown (patients usually decline any treatment)

medication is deemed appropriate, an empirical approach is advocated. When parasomnias are part of a specific neurological disease, such as a parkinsonian disorder, treatment is discussed in the respective chapter (e.g. chapter 9).

Diagnostic procedures and differential diagnosis

Needless to say, evaluation begins with an in-depth clinical interview with the patient and family members, if possible, especially if they sleep in the same bed or room. Table 16.3 outlines some particularly important questions to address. More formal algorithms such as the Frontal Lobe Epilepsy and Parasomnias scale (FLEP) are also available (see chapter 15). It is crucial to elucidate the frequency, duration, and timing of episodes with respect to the pre-dormitum, post-dormitum, first or second half of the night. Detailed history-taking will often allow a confident diagnosis without recourse to expensive and time-consuming investigations. Prompting the patient to make audio-video recordings at home may facilitate the diagnosis, often adding details that are missed in verbal descriptions given by relatives.

Video-polysomnograph monitoring with extended EEG, EMG, and autonomic function recording remain necessary in complex cases or where there is doubt. Clearly, the more frequent the events, the more likely video-polysomnography will be of value.

In distinguishing epileptic from non-epileptic events, it is important to remember that the absence of surface EEG discharges in no way rules out an epileptic etiology, especially in the case of NFLE. It is sometimes particularly difficult to distinguish an arousal disorder (sleep terrors and sleepwalking) from an event due to NFLE (paroxysmal arousal, nocturnal paroxysmal

**Table 16.3** Screening questions to help the differential diagnosis of epileptic nocturnal frontal lobe seizures and parasomnias

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How would you describe the episode in detail?
What kind of motor behaviour is associated with the episodes (quiet, violent, purposeful or bizarre)
Do abnormal movements or postures occur during the episodes?
Are episodes stereotyped?
How long do the episodes last?
In which part of the night do the episodes appear?
How frequently do the episodes occur (how many times per night, week or month)?
When did the episodes start (infancy, adolescence, adulthood)?
Have the episodes changed over the years? (unchanged, tended to disappear, frequency increased)
Is the episode clearly recalled?
Are you sleepy during the day?

---

dystonia, and epileptic nocturnal wandering) on the basis of history-taking alone. This is why NFLE has previously been confused with arousal disorders until polysomnography was routinely performed alongside audiovisual recordings. This also explains why some still consider subjects with “agitated somnambulism” a variant of sleepwalking and not a form of epileptic nocturnal wandering. In our experience an epileptic origin should always be suspected when faced with an account or video-recording of “agitated somnambulism” [21]. Paroxysmal arousals and NPD are very frequent in ENW and may therefore be picked up during an audiovideo home recording.

REM parasomnias do not usually pose diagnostic problems. REM sleep behavior disorder affects predominantly elderly males with a peak onset in the second half of the night, unlike arousal disorders and ENW. Consistent and aggressive dream recall is also very suggestive. Equally, nightmares and sleep paralysis are easy to recognize.

When a patient consults a sleep specialist because he occasionally bites his tongue or lips during sleep, causing cuts or painful injuries, the diagnosis may not be obvious. The patient may well have experienced a previously undiagnosed generalized seizure although NFMM should also be considered. In the former, detailed history-taking will usually disclose that the patient feels exhausted with aching muscles on the morning following the episode. In addition, collaborative information from family or bed partners may confirm concerns over muscle jerks or noisy breathing in deep sleep. In NFMM, only close bed partners may recognize that the patient sometimes has teeth biting episodes lasting several seconds.

As a general rule, with rare exceptions, myoclonic events arising in the pre-dormitum are non-epileptic in origin (sleep starts, periodic limb movements/nocturnal myoclonus, propriospinal myoclonus), whereas those occurring in the post-dormitum during or just after awakening are almost invariably epileptic (e.g. JME).

### Key points

- The distinction between nocturnal seizures and non-epileptic events (mainly parasomnias) can be difficult although a clear history is usually sufficient for a confident diagnosis.
- It is useful to make a distinction between events happening in the “pre-dormitum,” sleep itself, and the “post-dormitum.”
- Brief motor phenomena at the point of sleep onset are very rarely epileptic in nature in contrast to those occurring soon after waking.
- If “agitated somnambulism” has been diagnosed, the rare possibility of epileptic nocturnal wandering should be considered in some cases.
- Video-polysomnograph recording, ideally in the home environment, can be very helpful where there is diagnostic doubt.

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## **PART VI**

# Trauma and Stroke

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## CHAPTER 17

# Sleep-wake disorders following traumatic brain injury

*Christian R. Baumann*

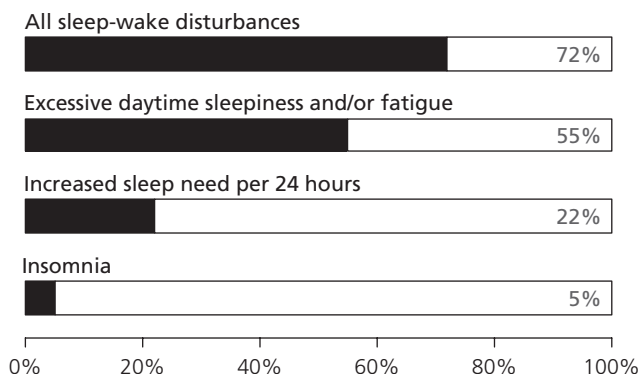
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### Introduction

Traumatic brain injuries are caused by a physical trauma such as a blow to the head or a penetrating head injury. Traumatic brain injuries are clinically classified as mild, moderate or severe, depending on the duration of loss of consciousness and associated amnesia. In the literature, the annual incidence rates for traumatic brain injury range between 7.3 and 300/100,000 [1–3]. In the United States, for example, an estimated 1.6 million people sustain traumatic brain injury each year, accounting for 52,000 deaths and 80,000 patients suffering from irreversible neurological impairment [1,2]. Persisting deficits after traumatic brain injury commonly include neuropsychological and psychiatric symptoms, as well as sleep-wake disturbances [3]. In this chapter the most important sleep-wake consequences of head injury are separately discussed, with diagnostic and therapeutic suggestions for each problem.

### Clinical epidemiology

Clearly, traumatic brain injuries are highly heterogeneous with respect to the type, localization, and severity of trauma, posing significant restrictions on systematic clinical studies. The few published studies on post-traumatic sleep-wake disturbances (SWD) have mostly been performed in retrospective settings. It is therefore difficult to make conclusions on epidemiological issues. The first systematic and prospective studies on post-traumatic sleep-wake disturbances have been published only very recently. In 65 consecutive patients, sleep-wake disturbances were systematically recorded by means of interviews, questionnaires and electrophysiological sleep



**Figure 17.1** Frequency of traumatic brain injury-related sleep-wake disturbances in the first prospective study in 65 consecutive traumatic brain injury patients. Sleep-wake disturbances were assessed and characterized by interviews, questionnaires, sleep laboratory examinations including polysomnography, Multiple Sleep Latency Test and actigraphy.

laboratory examinations 6 months after the traumatic brain injury [4]. In 47 patients (72% of the population), trauma-related sleep-wake disturbances were identified which were not present prior to the accident (figure 17.1). Sleep-wake disturbances occurred irrespective of the localization or the severity of the trauma. The most prevalent sleep-wake disturbances following traumatic brain injury was impaired daytime vigilance (EDS and fatigue in 55%). An increased sleep need per 24 hours ( $\geq 2$  hours more than before traumatic brain injury) was also common (observed in 22%). On the other hand, insomnia was found in only 5% of patients with traumatic brain injury. Another prospective clinical and sleep laboratory study in 87 patients at least 3 months after traumatic brain injury found sleep-wake disturbances in 46% of the examined population, with EDS as the most common finding (25%) [5]. The long-term outcome of sleep-wake disturbances after traumatic brain injury has not been systematically examined yet.

## Excessive daytime sleepiness

### Clinical features

With regard to impaired vigilance, there seem to be two potentially separable problems that can occur after traumatic brain injury. On the one hand, there is EDS, characterized by recurrent lapses into sleep during the daytime, which are often of relatively short duration. On the other hand, some patients develop an increased total amount of sleep over 24 hours, with long nocturnal sleep time and long subsequent daytime naps. In this chapter, we use the term “hypersomnia” to refer to the latter type. The two types of sleep disturbance may be equivalent to idiopathic



hypersomnia with and without long sleep time (see chapter 19), although this has not been specifically addressed.

As early as 1983, Guilleminault and colleagues highlighted the potential importance of recognizing EDS as a residual symptom after traumatic brain injury [6]. In their study, they found sleep apnea in a significant portion of their sleepy traumatic brain injury patients. More recent prospective data, however, have shown that in a majority of patients with traumatic brain injury, post-traumatic EDS cannot easily be explained by underlying sleep-wake, neurological, or other disorders [4]. Rather, it appears that post-traumatic EDS may be directly related to the neuronal injury itself. The precise underlying pathophysiology, however, is not known. A clear or simple association between traumatic brain injury characteristics (such as severity or localization of the trauma) and post-traumatic EDS has not been found [4,5]. Early studies revealed that hypothalamus and brainstem – both important regions in the regulation of sleep and wakefulness – are often damaged after traumatic brain injury [7,8]. The preliminary findings of mildly decreased cerebrospinal fluid levels of the wake-promoting hypothalamic neuropeptide hypocretin in sleepy traumatic brain injury patients, and of decreased numbers of hypocretin-producing cells in the hypothalamus of deceased traumatic brain injury patients, suggest that traumatic lesions to wake-promoting neuronal systems may contribute to post-traumatic EDS [4, unpublished data].

Although the recent hypocretin findings in traumatic brain injury suggest a relation with narcolepsy, the existence of “true” post-traumatic narcolepsy remains a matter of debate however. Despite previous studies suggesting that narcolepsy might be common after traumatic brain injury [5,9], narcolepsy with typical, unequivocal cataplexy is exceedingly rare after traumatic brain injury. This is important, as the diagnostic criteria for narcolepsy without cataplexy are mainly based on Multiple Sleep Latency Test findings, which are hampered by suboptimal specificity [10].

## Diagnosis and management

Excessive daytime sleepiness can be identified during the clinical interview (table 17.1; see also chapter 19) or with questionnaires such as the Epworth Sleepiness Scale or the Karolinska Sleepiness Scale. The Multiple Sleep Latency Test remains the most important objective laboratory technique to detect the presence of EDS [4,5,11]. It is always important to consider and rule out other etiologies, especially nocturnal sleep disturbances such as sleep-disordered breathing or periodic limb movements during sleep. Furthermore, other disorders (e.g. hypothyroidism) should be ruled out by appropriate tests.

Excessive daytime sleepiness impairs daytime functioning and quality of life of patients with traumatic brain injury [4,11] and, although

**Table 17.1** Useful “probes” for sleep-wake disturbances after traumatic brain injury*Excessive daytime sleepiness:*

Since the trauma,

- do you fall asleep unintentionally during the day?
- do you have difficulties performing activities because of lapses into sleep, including driving a car?
- do you have an increased need to take daytime naps? If yes, how long do these last?

*Hypersomnia:*

Since the trauma,

- how many hours do you sleep per 24 hours (including daytime naps)?
- has this amount changed compared to before the trauma?
- do you have difficulties waking up in the morning?

*Fatigue:*

Since the trauma,

- do you often feel a lack of energy, or physical and mental tiredness?
- are you easily exhausted?

*Insomnia:*

Since the trauma,

- do you have difficulties initiating or maintaining sleep at night?
- do you feel your nocturnal sleep to be “unrestorative” or poor in quality despite adequate opportunity and circumstances for sleep?

*Circadian rhythm sleep disorder:*

Since the trauma,

- has your sleep-wake rhythm changed?
- do you perceive a tendency to go to sleep much earlier or later than before the trauma?
- do you perceive a tendency to awaken in the morning much earlier or later than before the trauma?

treatment is warranted, until now no specific therapy for post-traumatic EDS has been rigorously tested or approved. Modafinil is used to treat EDS in a variety of disorders. In contrast to initial encouraging case reports and small series, a recent study could not confirm a beneficial effect from modafinil on post-traumatic EDS [12]. The use of other neurostimulants such as methylphenidate or of activating antidepressants has not been studied, but might be worthwhile. Given the prevalence and consequences of post-traumatic EDS, further studies to delineate treatment strategies for sleepy traumatic brain injury patients are urgently needed.

## Hypersomnia

### Clinical features

Hypersomnia is defined by increased sleep need per 24 hours, and must be distinguished from EDS (increased daytime sleep propensity

with difficulties fighting sleep during waking hours). In the context of traumatic brain injury, a reasonable definition of hypersomnia could be an increased sleep need of more than 2 hours compared to the situation before the traumatic brain injury [4]. Studies on post-traumatic hypersomnia are sparse. In a prospective study in 65 patients with traumatic brain injury, most patients with post-traumatic sleep-wake disturbances suffered either from hypersomnia or from EDS and fatigue [4]. Furthermore, an association between severity of traumatic brain injury and the presence of hypersomnia was found [4]. In the light of these findings, one may hypothesize that hypersomnia, rather than EDS per se, is the primary sleep-wake disorder after traumatic brain injury. In other words, patients whose psychosocial environment allows extended sleeping times per 24 hours may avoid increased sleep propensity during daytime, whereas in patients who cannot compensate the increased sleep need, EDS may occur. This hypothesis is supported by the finding of increased EDS in patients between the ages of 30 and 50, whose social environment tends not to allow for longer sleeping times due to tight work schedules or families with young children, compared to hypersomnia seen in younger or older subjects [4].

## **Diagnosis and management**

Post-traumatic hypersomnia can be diagnosed using the clinical interview (table 17.1). A sleep log completed by the patient over 1–2 weeks can also be very helpful. An objective method to estimate total sleep time is wrist actigraphy. Actigraphy measures motor activity continuously over a defined period of usually 1–2 weeks. Patterns of sustained activity or absence of activity correlate well with wake and sleep periods, respectively.

Post-traumatic hypersomnia can be very difficult to treat. A specific treatment is not available. Psychostimulants may be attempted, but, in practice, efficacy is often disappointing.

## **Fatigue**

### **Clinical features**

Fatigue is a subjective experience, that may include such symptoms as a persisting lack of energy, exhaustion, physical and mental tiredness, or even apathy [13]. Although often quoted as an important symptom, definite conclusions regarding fatigue after traumatic brain injury cannot easily be drawn due to the inconsistent definitions of fatigue, the use of

a multitude of assessment scales that have not been validated properly in the few available studies, and the lack of an objective test.

Fatigue as assessed by the Fatigue Impact Scale and the Fatigue Severity Scale was found to be common in patients with traumatic brain injury [14]. Similarly, a recent study used the Global Fatigue Index and observed that fatigue is more common and pronounced in patients with traumatic brain injury compared to healthy controls [15]. The authors found associations with other symptoms such as pain, depression, and sleep-wake disturbances, but not with specific traumatic brain injury characteristics.

### **Diagnosis and management**

The pathophysiology of fatigue in general and of post-traumatic fatigue, in particular, is not known. Consequently, there are no laboratory tests to diagnose or assess fatigue. Besides structured interviews, there is a multitude of different fatigue assessment scales to diagnose and quantify fatigue. However, only few of them have been validated, mostly in small studies and for specific disorders. The Fatigue Severity Scale is one of the most commonly used self-report questionnaires to measure fatigue, and has recently been validated in a large sample [16]. A specific therapy of post-traumatic fatigue is not available. Treatment of concomitant depression, pain, or sleep-wake disturbances might help alleviate fatigue in patients with traumatic brain injury. In a recent study, modafinil failed to show beneficial effects on fatigue following traumatic brain injury [12]. In chronic fatigue syndrome, positive effects of specifically developed cognitive behavioral therapies have been reported several times, but data on post-traumatic fatigue is lacking.

## **Insomnia**

### **Clinical features**

Insomnia is defined as a chronic inability to fall asleep or remain asleep for an adequate length of time at night. Previous studies have yielded contradictory results on the prevalence of insomnia in patients with traumatic brain injury. A prospective study based on sleep questionnaires observed a high prevalence (30%) of insomnia symptoms in 50 patients after traumatic brain injury [17]. Furthermore, in a retrospective study comprising a population of 184 somnolent subjects who suffered a traumatic brain injury or head-neck trauma (whiplash injury), almost half of the patients reported additional disturbed sleep at night, mostly due to nocturnal pain [11]. Another study examined sleep-wake diaries of 63 patients with traumatic brain injury and 63 healthy controls. The major finding was an increased number of night-time awakenings and higher latencies from

wakefulness to sleep in patients with traumatic brain injury, particularly in those with mild injuries, anxiety, and depression [18]. In a questionnaire study, more than 50% of 452 patients with traumatic brain injury reported insomnia symptoms [19]. Risk factors associated with insomnia were milder injuries, higher levels of fatigue, depression, and pain. Similarly, 14 patients with traumatic brain injury were compared to 14 healthy good sleepers by the same group, and all subjective measures of sleep as assessed by questionnaires revealed significant sleep disturbances in the traumatic brain injury group [20]. The authors found, however, that traumatic brain injury patients with insomnia have a tendency to overestimate their sleep disturbance compared to objective (polysomnographic) measures of sleep. Of note, a prospective study including objective sleep laboratory tests has found insomnia in only 5% of patients [4]. Together, these studies suggest that insomnia may be relatively common, but also overestimated after traumatic brain injury.

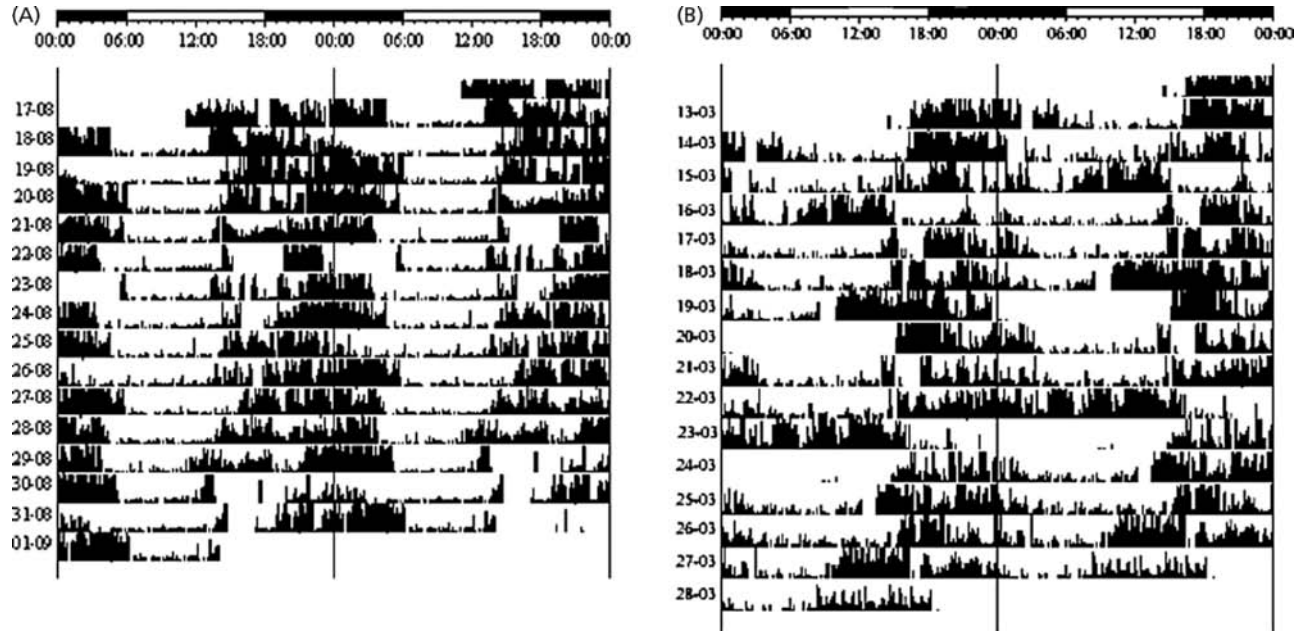
### **Diagnosis and management**

Post-traumatic insomnia appears to be related to depression and anxiety [17–20]. Screening for and subsequent treatment of psychiatric comorbidities should, therefore, always be performed in patients that complain of post-traumatic insomnia (table 17.1). Conventional hypnotic medications remain the most frequently used treatment for insomnia in clinical practice although issues remain over long-term use and with tolerance or side effects. A recent study suggested that psychological interventions including cognitive behavioral therapies for insomnia are a promising therapeutic strategy for traumatic brain injury patients [21].

## **Circadian sleep-wake disorders**

### **Clinical features**

Relevant information on potential circadian sleep-wake disorders following traumatic brain injury is scarce and rather inconclusive. Anecdotal reports on a post-traumatic delayed sleep phase syndrome have been published, but a study of 10 patients using questionnaires, sleep diaries, polysomnography, and saliva melatonin measurements failed to provide evidence of any shift in circadian timing of sleep subsequent to traumatic brain injury [22,23]. A recent study in 42 patients with minor traumatic brain injury with complaints of insomnia were examined by actigraphy, saliva melatonin, and oral temperature measurements [24]. The authors found circadian sleep-wake disorders in 36% of these patients. Two varieties were observed: delayed sleep phase syndrome and irregular sleep-wake pattern (figure 17.2). The observation of frequent circadian sleep-wake disorders following traumatic



**Figure 17.2** Actigraphy findings of a patient with delayed sleep phase syndrome (A) and a patient with an irregular sleep-wake pattern (B). The horizontal lines show the times of the day, the vertical lines distinguish between different days during a 2-week observation period. Sleep episodes are represented by periods with low or nonexistent movements (“white” areas), wake periods by continuous motor activity (“black” areas). Reproduced from Ayalon et al. [24] with permission from Lippincott, Williams & Wilkins.

brain injury supports the assumption that post-traumatic insomnia might be overestimated and in fact be an expression of a circadian rhythm disturbance.

## Diagnosis and management

The clinical diagnosis of circadian sleep-wake disturbances is based on a detailed interview (table 17.1), as well as on sleep diaries and actigraphy studies (figure 17.2). Treatments with melatonin or bright light, aiming to synchronize the sleep-wake cycle with the environmental dark-light cycle, are appropriate therapeutic strategies for these patients [24] (see also chapter 7).

### Key points

- Sleep-wake disturbances are common after traumatic brain injury, and may take on a variety of forms.
- Correlating either the severity or site of injury with subsequent sleep-wake symptoms is rarely possible.
- It is probably important to distinguish excessive daytime sleepiness (EDS; relatively short-lasting lapses into sleep during waking hours) from post-traumatic hypersomnia (an increased total sleep duration over 24 hours of more than 2 hours).
- Hypocretin levels may dip severely after head injuries but usually recover. The relation to sleep-wake disturbance needs clarification.
- Treatment strategies are limited. Evidence from clinical practice or the few available trials suggests that agents such as modafinil or conventional psychostimulants are worth trying but effects often disappoint.
- Insomnia appears not as common after traumatic brain injury as previously thought. It is typically associated either with pain or mood and anxiety disorders.

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## CHAPTER 18

# Sleep disturbances after stroke

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## Introduction

Among general neurologists, there currently appears little awareness of the frequency and impact of sleep-disordered breathing (SDB) and sleep-wake disturbances (SWD) after stroke and even less knowledge of how to manage these conditions. Both sleep-disordered breathing [1–4] and sleep-wake disturbances [5,6] are highly frequent, each being found in up to 50% of stroke patients. Recent data suggest that both sleep-disordered breathing and sleep-wake disturbances negatively affect short- and long-term functional outcome, length of hospitalization, and risk of recurrence [5,7–9]. It is reasonable to postulate, therefore, that early diagnosis and therapy of post-stroke sleep-disordered breathing and sleep-wake disturbances may have a favorable effect on stroke outcome. This chapter outlines the present knowledge about the role of sleep-disordered breathing and sleep-wake disturbances in stroke, analysing the presentation, prevalence, and clinical consequences of various sleep disturbances and providing recommendations for treatment.

## Clinical presentation and pathophysiological relevance

### Sleep-disordered breathing

#### Clinical presentation

Night-time symptoms of sleep-disordered breathing include insomnia, respiratory noises, irregular breathing, agitated sleep, shortness of breath, palpitations, and nocturia. In patients with severe hypoventilation, arousal

responses can be suppressed by increasing sleep debt and, in conjunction with cardiac arrhythmias, may lead to sleep-related death. Daytime symptoms of sleep-disordered breathing are headaches, fatigue, sleepiness, and concentration and memory deficits.

Approximately 50–70% of acute stroke patients exhibit sleep-disordered breathing, as defined by an apnea-hypopnea index (AHI)  $\geq 10/\text{h}$  [1–4, 10–16]. In general, no link was found between sleep-disordered breathing and stroke severity, topography, or presumed etiology [3,4,13,14], although some studies suggested that strokes with sleep-disordered breathing might be associated with macroangiopathy [17], persistent foramen ovale [18], and hemorrhagic strokes. The frequency of sleep-disordered breathing is similar in patients with transient ischemic attack (TIA) and stroke [1,2,10,19], suggesting that sleep-disordered breathing may be not only a consequence of brain injury but may reflect a pre-existing condition. The commonest form of sleep-disordered breathing in stroke patients is obstructive sleep apnea (OSA), caused by a cessation of nasal airflow due to upper airway collapse [1–4]. Occasionally, patients present with mixed breathing disturbances involving both OSA and central sleep apnea (CSA), sometimes resembling Cheyne-Stokes breathing (CSB) [1,2,20–22].

Central sleep apnea/Cheyne-Stokes breathing was first described in patients with bilateral strokes associated with disturbed consciousness or cardiorespiratory failure [23]. More recently, Cheyne-Stokes breathing presenting only during sleep has also been found in patients with preserved consciousness and unilateral strokes in the absence of overt cardiorespiratory dysfunction [10,21,22].

As stroke patients move from the acute to the subacute phase, sleep-disordered breathing and, in particular, central sleep apnea/Cheyne-Stokes breathing improve, suggesting that sleep-disordered breathing may be exacerbated by stroke. Nonetheless,  $\sim 50\%$  of patients still exhibit an apnea-hypopnea index  $\geq 10/\text{h}$ , 3 months after stroke [2,3,13,24].

### **Pathophysiological relevance**

Sleep-disordered breathing may predispose to vascular diseases, as emphasized in a recent statement paper from the American Heart Association [25]. This conclusion was based on several cohort [8,26] and population-based studies [9,27,28] which have shown that sleep-disordered breathing elevates the risk for stroke and death, besides that of myocardial infarcts and heart failure, with increased odds ratios even when data were corrected for established vascular risk factors.

The elevated risk is thought to result from hypoxia, intrathoracic pressure changes, and sympathetic activation [7,29]. These factors lead to inflammatory responses in the vasculature, endothelial dysfunction, atherosclerosis, arterial hypertension, platelet activation, and prothrombotic coagulation

changes [7,29]. Sleep-disordered breathing also predisposes to myocardial ischemia, left ventricular failure and cardiac rhythm abnormalities, all of which contribute to the risk for stroke [7,29]. Continuous positive airway pressure (CPAP) therapy potentially reverses the pathophysiological consequences of sleep-disordered breathing, improving arterial hypertension and presumably also vascular risk [7,29].

Several studies indicate that sleep-disordered breathing adversely affects early neurological evolution following stroke [20], hospitalization duration [30], and both short-term [20] and long-term [24,31] outcome. In a series of 120 patients, the presence of sleep-disordered breathing predicted a worse Barthel index and higher mortality at 6 months after stroke [32]. This finding was reproduced in other studies in patients with first-ever stroke or TIA, in which sleep-disordered breathing increased patients' mortality over several years [2,3]. Stroke recurrence has also been linked with the presence of sleep-disordered breathing [17]. Furthermore, the presence of recurrent nocturnal hypoxia has also been linked with poor rehabilitation outcome [33]. The detrimental effect of sleep-disordered breathing appears to be more pronounced for obstructive sleep apnea than for central sleep apnea [31].

## **Disorders of wakefulness**

### **Clinical presentation**

The clinical spectrum of post-stroke disorders of wakefulness includes hypersomnia (i.e. abnormal sleep propensity with increased sleep over 24 hours), excessive daytime sleepiness (EDS; an increased tendency to fall asleep during waking hours), and fatigue (physical exhaustion, lack of energy, tiredness) [7,34].

In a systematic study of 285 consecutive stroke patients, at  $21 \pm 18$  months after presentation, we observed hypersomnia in 27% of cases with sleep needs  $\geq 10$  hours/day, EDS in 28% with Epworth Sleepiness Scores  $\geq 10$ , and fatigue in 46% with fatigue severity scale scores  $\geq 3$ . Hypersomnia typically improves during the first months, whereas fatigue often persists into the chronic phase [35].

Post-stroke hypersomnia most often presents after striatal, thalamic, mesencephalic, upper pontine, and medial pontomedullary strokes. The most dramatic form of post-stroke hypersomnia is observed after paramedian thalamic stroke [34,36–38]. Patients typically present with sudden onset of coma. After eventual awakening, this group tend to exhibit severe hypersomnia and sleep-like behavior up to 20 hours/day, associated with attentional, cognitive, and memory deficits [38]. Hypersomnia generally improves over a period of months, whereas cognitive deficits often persist, particularly after predominantly left-sided or bilateral stroke [38]. Indeed, patients with bilateral strokes may report increased sleep needs for several years.

Hypersomnia with hyperphagia [39] and symptomatic narcolepsy (hypersomnia with cataplexy-like episodes, hallucinations, sleep paralysis, and low cerebrospinal fluid hypocretin-1 levels) [40,41] have been observed after multiple cerebral and hypothalamic strokes, respectively.

### **Pathophysiological relevance**

Excessive daytime sleepiness and fatigue are associated with neuropsychiatric symptoms such as depression and anxiety as well as cognitive disturbance, particularly reduced attention. All these have a negative impact on stroke rehabilitation, daily functioning, and quality of life [5]. Post-stroke fatigue is an independent predictor of independence and death, as shown in a large cohort of 8194 stroke patients [42].

## **Insomnia**

### **Clinical presentation**

Insomnia is defined by difficulty initiating or maintaining sleep, early awakenings, insufficient sleep quality, and daytime fatigue. Post-stroke insomnia is usually associated with the complications of stroke. Environmental factors, including noise, light, and intensive care monitoring, may play a role together with comorbidities such as cardiac failure, sleep-disordered breathing, and infections.

Similar to hypersomnia, post-stroke insomnia is common. In a systematic study of 277 consecutive patients insomnia was found in the first few months after stroke in 57% of patients [5]. In 18%, insomnia appeared *de novo* after the stroke [5]. In view of the known consequences of impaired sleep such as daytime fatigue and cognitive problems, insomnia might be expected to impair stroke recovery. Systematic studies supporting this hypothesis are, however, lacking.

Occasionally, insomnia may be related directly to brain damage, mostly in the brainstem. Patients with altered or loss of sleep EEG patterns lasting over several months have been reported particularly after pontine and pontomesencephalic strokes [43].

### **Pathophysiological relevance**

After stroke, insomnia accentuates fatigue, EDS, and attention, memory, and cognitive problems. These factors are likely to have an unfavorable influence on stroke outcome and recovery.

## **Sleep-related movement disorders**

### **Clinical presentation**

Restless legs syndrome (RLS) is characterized by an urge to move the limbs that is particularly pronounced in the evening hours. Restless legs syndrome is often associated with periodic limb movements during sleep

(PLMS). While RLS/PLMS is frequently an idiopathic condition, symptomatic RLS/PLMS following stroke has been described. In a cohort of 137 patients that were examined 1 month after their stroke, Lee et al. [6] reported a RLS prevalence of 12%. Restless legs syndrome was observed mainly in patients with pontine, thalamic, basal ganglia, and corona radiata infarcts. About two-thirds of patients had bilateral RLS symptoms; one-third had unilateral complaints contralateral to the stroke [6]. Restless legs syndrome appeared within 1 week post-stroke and was frequently accompanied by PLMS.

### **Pathophysiological relevance**

Restless legs syndrome and periodic limb movements during sleep have a potentially significant influence on quality of life. In general, RLS/PLMS might also affect life expectancy, as suggested by a recent Swedish population-based study following up 5102 subjects (30–65 years) over 20 years [44]. In a multivariate analysis adjusted for age, sleep time, lifestyle factors, medical conditions, including diabetes and hypertension, and depression, women with RLS and daytime sleepiness had an excess mortality compared with women without RLS and daytime sleepiness [44].

## **Diagnosis and treatment**

### **Sleep-disordered breathing**

#### **Diagnosis**

Sleep-disordered breathing can be diagnosed by respiratory polygraphy, in which nasal airflow and thoracic and abdominal respiratory movements in addition to capillary oxygen saturation are monitored. Polysomnography offers additional information on sleep architecture, but is more expensive and less commonly available in acute settings. It should therefore be reserved for complex or unclear situations. Based on nasal airflow, respiratory movements, and oxygen desaturation recordings, various forms of sleep-disordered breathing can be defined, including obstructive sleep apnea, central sleep apnea, or Cheyne-Stokes breathing. The apnea-hypopnea index and the number and severity of oxygen desaturations are indicators of the severity of sleep-disordered breathing. Using a cost-effectiveness model, Brown et al. [45] found that screening for sleep-disordered breathing is cost-effective in stroke patients as long as CPAP treatment improves patient utilities by  $>0.2$  for a willingness-to-pay \$50,000 per quality-adjusted life year or by  $>0.1$  for a willingness-to-pay \$100,000 per quality-adjusted year.

### Treatment

Sleep-disordered breathing treatment in stroke patients potentially represents a clinical, technical, and logistical challenge. Therapeutic strategies should always address the prevention and early treatment of secondary complications such as respiratory infections. Cautious use of sedation is also important given the negative effects on nocturnal breathing. Patient positioning in the acute phase may also influence oxygen saturation. Continuous positive airway pressure is the treatment of choice for patients with obstructive sleep apnea, and they can usually be treated within days after stroke [3]. Since sleep-disordered breathing improves in the first weeks, intelligent CPAP systems which allow automatic titration of CPAP pressure may be preferable in this situation.

Compliance with CPAP has been reported to be as high as 70% in the rehabilitation setting [46]. Other groups working in the acute stroke setting, however, reported lower percentages [3,13,47–50]. In a randomized trial of stroke patients with severe sleep-disordered breathing ( $AHI \geq 30/h$ ) the CPAP usage was very low with a mean of 1.4 hours/night [47]. In our experience, only ~50% of stroke patients with sleep-disordered breathing can be treated in the acute phase, and only half of these patients stay on CPAP in the long run [3]. Compliance is certainly influenced by the spontaneous improvement of sleep-disordered breathing and by the absence of daytime sleepiness in many patients. In addition, compliance can be expected to be a issue in stroke patients with mask problems related to severe facial or bulbar weakness, severe motor deficits causing problems when handling the CPAP mask, confusional states, dementia, aphasia, and anosognosia.

In patients with central apneas and Cheyne-Stokes breathing, improvement can be achieved with oxygen therapy [23]. Novel methods of ventilatory support such as adaptive servo-ventilation may also be considered. Tracheostomy and mechanical ventilation may become necessary in patients with severe central hypoventilation.

One outcome study noted an improvement of subjective well-being and night-time blood pressure values in a group of 41 and 16 patients, respectively, with stroke and sleep-disordered breathing, who were treated with CPAP over 10 days [46]. Another study in 51 patients with stroke and an  $AHI \geq 20/h$  reported that 29% of stroke patients were still on CPAP after 1 month [48]. The large majority continued their treatment over 18 months. This group had a significantly lower incidence of new vascular events.

## Disorders of wakefulness

### Diagnosis

Most sleep-wake disturbances are relatively easy to recognize on clinical grounds. Not uncommonly, the presence or severity of sleep-wake

disturbances is first fully appreciated when patients leave the hospital. The correlation of post-stroke sleep-wake disturbances with changes in the sleep EEG is not very good, particularly when vascular brain damage includes thalamocortical and cortical structures involved in wakefulness and EEG generation [37,38].

In patients with post-stroke hypersomnia, the sleep EEG may reveal a reduction or, less commonly, a proportional increase in non-REM or REM sleep. Particularly in supratentorial strokes, the Multiple Sleep Latency Test, which is widely used to evaluate sleep propensity, may be inadequate for assessing post-stroke EDS [38]. Actigraphy may be helpful to estimate changes in sleep-wake rhythms and sleep/rest needs [38], although a differentiation between sleep and apathy or inactivity may be difficult.

### **Treatment**

Treating post-stroke hypersomnia is often unsatisfactory and evidence is confined to single case studies. Improvement of apathy and pre-sleep behavior has been reported in patients with paramedian thalamic stroke following 20–40 mg bromocriptine [36]. A favorable influence on early post-stroke rehabilitation was described both after levodopa (100 mg/d [51] and methylphenidate (5–30 mg/d) [52], an effect that may at least in part be related to improved alertness. A clear-cut improvement of alertness with 200 mg modafinil was observed in a patient with bilateral paramedian thalamic stroke [43]. Treatment of stroke-associated depression with stimulating antidepressants may also improve hypersomnia.

## **Insomnia**

### **Diagnosis**

As with hypersomnia, the recognition of post-stroke insomnia requires careful clinical observation. Actigraphy may help to document and quantify changes in sleep-wake rhythms and the sleep/rest cycle although polysomnography rarely adds useful information.

### **Treatment**

Post-stroke insomnia can be improved by the simple measure of placing patients in quiet rooms at night and protecting them from noise and light. Increased light exposure during the day may also help. When necessary, temporary use of hypnotics that are relatively free of cognitive and muscle relaxant effects, such as zolpidem or zopiclone, is recommended. However, it should be kept in mind that benzodiazepines may provoke neuropsychological deficits and even result in the re-emergence of motor symptoms [53].

Sedative antidepressants may improve post-stroke insomnia. In a study of 51 stroke patients, 60 mg/d of mianserin resolved insomnia symptoms

more than placebo, even in patients without depression [54]. In patients clearly exhibiting depressive symptoms, antidepressants should be considered for their positive effects on insomnia.

## Sleep-related movement disorders

### Diagnosis

Restless legs syndrome/periodic limb movements during sleep is diagnosed by clinical observation, actigraphy, or polysomnography. When present, RLS/PLMS is found bilaterally in slightly more than half of the patients with the others exhibiting RLS/PLMS contralateral to the stroke [6].

### Treatment

Treating 17 patients with stroke-related restless legs syndrome with dopamine agonists (ropinirole 0.25–1 mg/d, pramipexole 0.125–0.5 mg/d), Lee et al. [6] reported marked relief in 15 and mild improvement in two. All patients had persistent restless legs syndrome until the end of the study period, indicating that most patients would potentially benefit from treatment [6]. Eventual spontaneous improvement was noted in only 4 out of 17 patients, allowing the authors to terminate drug prescription [6]. All other patients remained on dopaminergic drugs.

### Key points

- Sleep-wake disturbances including sleep-disordered breathing, notably obstructive sleep apnea, are very common following all types of stroke.
- Limited evidence suggests that early recognition and treatment of sleep-disordered breathing improves stroke outcome and reduces risk of recurrence.
- Fatigue, hypersomnolence, or insomnia frequently affect stroke victims. Such symptoms arise either as an indirect effect of the stroke and concomitant hospitalization or sometimes as a direct consequence of cerebral damage in areas involved in sleep-wake control.
- Restless legs syndrome may be common after subcortical strokes and be worthy of treatment. The dopaminergic drugs used in idiopathic restless legs syndrome appear effective.

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**PART VII**

Other Neurological  
Disorders

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## CHAPTER 19

# Hypersomnias of central origin

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### Introduction

Excessive daytime sleepiness can be an incapacitating symptom, but is not always recognized as such. Especially in the young, napping at inopportune times is often dismissed as laziness or as a consequence of "overdoing it." This is, in part, due to the fact that bystanders often consider themselves experts, having experienced daytime sleepiness as a result of a bad or reduced nocturnal sleep. On the other hand, patients themselves have sometimes difficulty describing sleepiness, often mentioning "fatigue" or "lack of energy." In such situations, it is crucial for doctors to ask the key question: "Do you fall asleep unintentionally during the day?"

When people have the opportunity to obtain nocturnal sleep of sufficient duration, unwanted daytime sleep episodes are pathological and warrant further assessment [1]. Most often, significant daytime sleepiness is caused by nocturnal sleep disorders, such as sleep-disordered breathing. Occasionally, it can be a symptom of another (neurological) disorder, such as Parkinson's disease. Secondary hypersomnias vary widely in their pathogenesis and include not only neurodegenerative disorders but immunological, (para)neoplastic, and vascular pathology as well. These disorders are discussed in the chapters devoted to the related disease mechanism. What remains is a rather heterogeneous group of primary hypersomnias, or "hypersomnias of central origin" according to the second edition of the *International Classification of Sleep Disorders* [2]. Narcolepsy is the prototypical disease in this category but a wide range of disorders, including idiopathic hypersomnia and periodic hypersomnias such as the Kleine-Levin syndrome, are included.

## Definition and classification

The point at which sleepiness is pathological is not clearly defined in the literature. Originally, the term “hypersomnia” was reserved for conditions in which there was an increase in the total amount of sleep over a 24-hour period [3]. However, that is not always the case in disorders with daytime sleepiness as the core symptom. For example, because of disrupted overnight sleep, patients with narcolepsy often have only marginally increased total sleep times, despite multiple daytime sleep episodes [4]. For the symptom of unwanted daytime sleep periods without a clear increase in total sleep time, the term “excessive daytime sleepiness” (EDS) has been coined. However, EDS and hypersomnia are often used interchangeably, and not in the strict sense. In fact, ICSD-2 *groups* the various disorders – including narcolepsy – under *hypersomnias* of central origin (see table 19.1). To make matters even more confusing, two forms of “idiopathic hypersomnia” are discerned: one with and one without a “long sleep time.” From this perspective, it may be justified to use the term “hypersomnia” to denote a pathological condition or disease entity, and EDS to describe a symptom. At the very least, it underscores the necessity of describing the patient’s complaints in specific detail, including aspects such as the habitual amount of sleep during the day, sleep inertia in the morning, and length of daytime naps.

Hypersomnias of central origin include a range of different disorders (table 19.1). In this chapter, we will discuss the most important ones. General emphasis is put on narcolepsy, as the prototype sleep disorder

**Table 19.1** Hypersomnias of central origin, according to ICSD-2

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Narcolepsy with cataplexy*
Narcolepsy without cataplexy*
Narcolepsy due to medical condition*
Narcolepsy, unspecified
Recurrent hypersomnia
Kleine-Levin syndrome*
Menstrual-related hypersomnia
Idiopathic hypersomnia with long sleep time*
Idiopathic hypersomnia without long sleep time*
Behaviorally induced insufficient sleep syndrome*
Hypersomnia due to medical condition*
Hypersomnia due to drug or substance
Hypersomnia not due to substance or known physiological condition (nonorganic hypersomnia)
Physiological (organic) hypersomnia, unspecified

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\*Discussed in this chapter.



about which most is known. Idiopathic hypersomnia is another important category, with two distinct subtypes. Behaviorally induced insufficient sleep syndrome is not a central hypersomnia, *per se*, but an important differential diagnosis for narcolepsy or idiopathic hypersomnia. Kleine-Levin syndrome is a rare but fascinating form of recurrent hypersomnia with fairly specific diagnostic and therapeutic aspects [5]. Hypersomnia can also be caused by another medical (neurological) condition. Important disorders associated with secondary hypersomnia include parkinsonian disorders, brain trauma, (auto)immune or paraneoplastic disease, and cerebrovascular disorders. These are all covered in other chapters. A number of neurodevelopmental or genetic disorders are often associated with central hypersomnia. These include the Prader-Willi syndrome, Niemann Pick type C disease, Norrie's disease and Moebius syndrome [6,7]. Only Prader-Willi syndrome will be mentioned in any detail, given the rarity of these other conditions.

## **Clinical epidemiology**

### **Narcolepsy**

The prevalence of the various central hypersomnias is not well established. Most studies have focussed on narcolepsy, with prevalence figures ranging from 0.02% to 0.18% of Western populations [8]. Men and women are affected equally. In most patients, symptoms present in adolescence, between 15 and 25 years of age. Importantly, studies have shown that the time between first symptoms and final diagnosis is often more than 7 years [9]. Furthermore, when looking back, patients often report having had symptoms at an earlier age, but mild enough not to raise the suspicion of a disease process. Sometimes, narcolepsy can develop at a particularly young age, even before 10 years. Recently, reports of young-onset narcolepsy have markedly increased, perhaps suggesting that previous age-at-onset estimates were in fact too high.

### **Idiopathic hypersomnia**

There have been no formal prevalence studies for idiopathic hypersomnia, especially for the separate subtypes with and without long sleep time. Some case series suggest one case of idiopathic hypersomnia with long sleep time for every 10 patients with narcolepsy in a sleep center. Studies are hampered by the fact that the only available diagnostic test (the MSLT, see chapter 3) is neither particularly sensitive nor specific.

### **Recurrent hypersomnia – Kleine-Levin syndrome**

Kleine-Levin syndrome is regarded as very rare, with only 186 published cases in the literature and no formal prevalence studies. However,

published cases may be biased towards “full-blown” or classical cases, with intermittent hypersomnia, cognitive disturbances, megaphagia, *and* hypersexuality [5,10]. Although it seems likely that mild forms, characterized mainly by periodic hypersomnolence, are more prevalent, these patients are not routinely encountered in clinical practice. The classical descriptions of the “full phenotype” suggest an over-representation of males with an estimated male/female ratio of 4:1. When periodic hypersomnia is the sole symptom, however, males and females seem to be much more equally affected.

### Behaviorally induced insufficient sleep

No formal prevalence studies have been carried out. There is a clinical impression that adolescents are more susceptible, probably due to a combination of high sleep need and social pressure to delay the sleep phase.

## Signs and symptoms

### The history of sleepiness

Obviously, an abnormal level of sleepiness is the core feature of the various hypersomnias of central origin. As discussed elsewhere in this book (e.g. chapters 1, 3, 17), there remains semantic confusion between symptoms such as hypersomnia, drowsiness, sleepiness, EDS, and so forth. Therefore, a careful and focussed history is paramount (chapter 1 and table 19.2). First, one has to establish if there is true abnormal sleepiness. Often, patients report sleepiness as fatigue. The core feature of excessive

**Table 19.2** Topics to cover in the clinical interview (see also chapter 1)

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<i>Is there EDS?</i> Separate from e.g. fatigue
<i>Age at onset</i> , circumstances at onset (trauma, etc.)
<i>Pattern and severity of EDS</i> : Continuous feeling of sleepiness, sleep “attacks,” circumstances, interference with daily life. Duration of sleep episodes. Planned naps. Sleep episodes refreshing? Periodicity of symptoms
<i>Automatic behavior</i> , memory complaints, concentration problems
<i>Night-time sleep</i> : Habitual sleep duration and sleep-wake timing. Sleep inertia. Signs of nocturnal sleep disorders
<i>Associated symptoms</i> , especially:
<b>Cataplexy</b> : pattern of weakness, duration, triggers, etc.
<i>Hypnagogic hallucinations</i> : frequency, content, impact
<i>Sleep paralysis</i> : frequency, duration
<i>Body weight/eating patterns</i> : weight increase, “craving,” night eating
<i>Mood disturbances</i>
<i>Psychosocial aspects</i> : social interactions, school, work, driving

---

sleepiness is the fact that people actually fall *asleep* during the day such that unintentional daytime naps are the single most distinguishing feature.

The *pattern* of sleepiness should be defined. How often do sleep episodes occur? Are there differences between days? Are episodes short (5–10 minutes) and refreshing, or extended (1 hour or more) and non-refreshing? Does a patient take planned naps, and, if yes, what is the effect? Is there a continuous feeling of sleepiness between sleep episodes, or is the patient (relatively) awake in between? In the morning, does the patient feel refreshed or not? Are there signs of sleep inertia (sleep drunkenness)? Are there any influencing factors? Are there differences at weekends or on holidays, for example? Is there a periodical pattern of sleepiness?

Automatic behavior may be a consequence of lapses in vigilance, although the patient does not overtly fall asleep. It is often reported in narcolepsy but is almost certainly present in other hypersomnias. Typical examples include reading back written text, only to find it illegible or about a completely different subject. Rarer, but perhaps more specific instances include bizarre or inappropriate actions such as putting the laundry in the fridge.

Fully exploring the nature of the complaint of sleepiness often gives diagnostic clues which can then be further refined on the basis of associated symptoms.

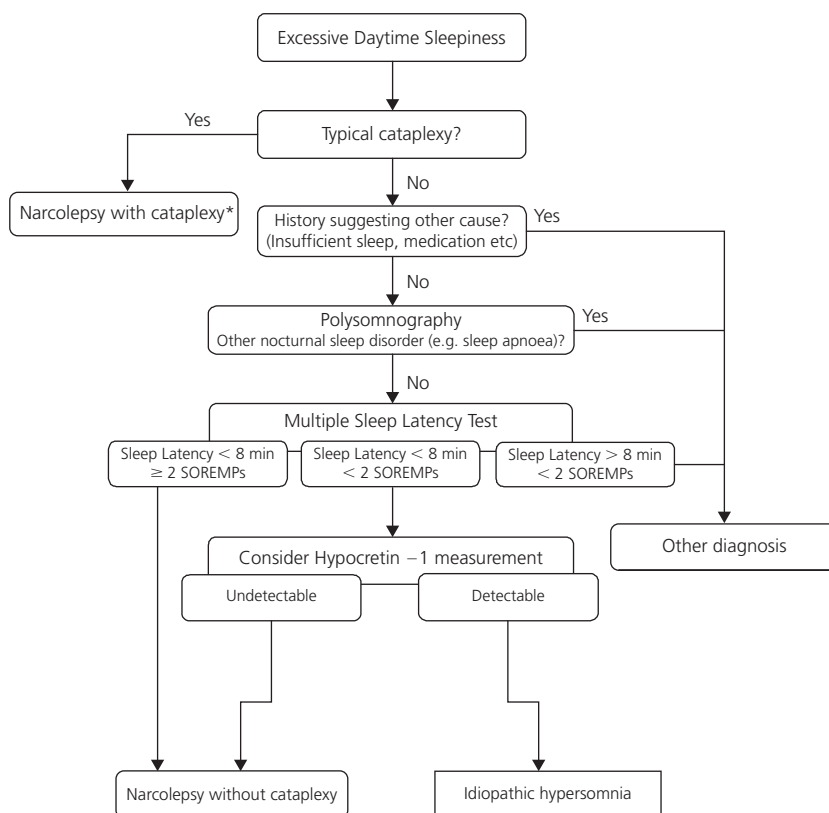
## **Narcolepsy**

### **Core symptoms**

Narcolepsy is predominantly characterized by two core symptoms: EDS and cataplexy [11,12]. Other symptoms that belong to the classical “tetrad” are hypnagogic hallucinations and sleep paralysis. Importantly, fragmented night-time sleep is nowadays regarded as a core symptom, and may sometimes even be the most bothersome aspect to patients. Recently recognized associated features include metabolic disturbances that can produce obesity and eating disorders [13,14]. Memory and cognitive complaints, especially in attentional domains, are common. Based on specific findings from ancillary sleep studies, a form of narcolepsy without cataplexy is recognized, although this may overlap with idiopathic hypersomnia (see “Diagnostic procedures” and figure 19.1).

### **Sleepiness**

The sleepiness in narcolepsy is typically characterized by relatively short and refreshing sleep episodes. In between sleeps, patients may have seemingly normal vigilance, but lapses are common. The sleepiness may be truly imperative but usually patients can postpone sleep for a while, for example, by engaging in physical activity. Sudden “sleep attacks”



**Figure 19.1** Diagnostic flowchart when narcolepsy is suspected in a patient with EDS.

\*Confirm with Multiple Sleep Latency Test or hypocretin-1 measurement.

without any recognized prior warning of sleep are certainly possible, but relatively rare. Although the patterns described are typical, exceptions do occur. For example, long daytime sleep episodes are described or sometimes there is a continuous feeling of sleepiness with superimposed lapses into sleep itself.

### Cataplexy

Cataplexy is the most specific symptom of narcolepsy and in combination with EDS is virtually pathognomonic for the disorder [15]. In its typical form, cataplexy shows as attacks of bilateral muscle weakness with preserved consciousness, triggered by an emotional context. Cataplexy can affect all skeletal muscles except those subserving respiration and eye movements. Attacks can be complete, causing the patient to slump to the ground. However, cataplexy is often partial. Preferential sites for partial cataplexy include the face (with dropping of the jaw and/or articulation problems), the neck (with dropping of the head), and the lower legs

(buckling of the knees). Although attacks start suddenly, they usually progress over a few seconds and are not immediate. This usually enables the patient to break the fall, making injuries rather uncommon. The duration of cataplexy is generally short with most attacks lasting only seconds. Attacks longer than a minute or two should prompt the suspicion of disorders other than cataplexy although they can sometimes be caused by a succession of several attacks when the trigger is continuously present. The most common trigger for cataplexy is mirth, or the expression of mirth: laughter. However, many other emotions can trigger cataplexy, such as surprise, anger, frustration, elation, and so on. Because a feeling of weakness in the knees when laughing is quite prevalent in the normal population [16], the additional presence of other triggers makes a diagnosis of cataplexy more specific. Note that a certain amount of relaxation is necessary for patients to experience cataplexy. Cataplexy is therefore not often encountered in the consultation room and attempts to provoke episodes are usually fruitless. When one witnesses a cataplexy attack, it is useful to assess muscle tone and bring out the reflex hammer: cataplexy (even when only partial) is accompanied by a loss of deep tendon reflexes.

### **Associated symptoms**

Hypnagogic hallucinations are very vivid dream-like experiences around sleep onset. When occurring around awakening, the term hypnopompic is used. The experiences can be extremely life-like and patients sometimes have to check retrospectively whether an event happened for real or not. This feeling of reality is reinforced by the fact that often a combination of the actual environment and the dream is present. Hypnagogic hallucinations are typically “multimodal,” combining visual, auditory, and tactile modalities. Sleep paralysis occurs during sleep onset or during awakening. The patient is conscious, but unable to move at all. In contrast to cataplexy, there is no defined trigger and attacks are prolonged, sometimes lasting up to 10 minutes. It is important to realize that sleep paralysis may occur with a low frequency in the normal population. Narcolepsy is often associated with a clear increase in body mass index; often weight increases around the onset of the other symptoms. Many patients report night-time eating behaviors and sometimes “carbohydrate craving” [13].

Concentration difficulties and memory problems are commonly reported. Formal testing often yields normal results, implying that these symptoms are most likely due to (micro)sleep episodes or deterioration in vigilance levels when sustained levels of concentration are required.

### **Idiopathic hypersomnia**

Historically, two forms of idiopathic hypersomnia have been described. One type is characterized by a normal amount of night-time sleep and

relatively short, refreshing daytime sleep episodes [17]. In other words, the pattern of sleepiness closely resembles that of narcolepsy, but no cataplexy is present, and MSLT testing does not show sleep-onset REM periods (see “Diagnostic procedures”). In ICSD-2, this form is now called idiopathic hypersomnia without long sleep time and is most often mentioned in literature from America [2].

The other form of idiopathic hypersomnia stems more from the “European school.” It has a rather typical symptom complex and total amounts of sleep over 24 hours are increased, with a long nocturnal sleep episode (usually of more than 10 hours) [3]. Patients do not feel refreshed in the morning, have significant difficulty waking up, feeling groggy and less vigilant for some time after awakening (“sleep inertia”). Daytime sleep episodes tend to be long (around an hour or even more) and are unrefreshing. This form is now classed as idiopathic hypersomnia with long sleep time [2].

### **Hypersomnia in neurodevelopmental syndromes**

Patients with Prader-Willi syndrome often display pronounced daytime sleepiness which cannot be explained by common disorders such as obstructive sleep apnea [6,7]. It is assumed there is specific hypothalamic pathology in Prader-Willi patients given their abnormal appetite regulation and sleep problems. Hypocretin levels are generally normal and the notion of hypocretin “resistance” has been raised [18].

### **Recurrent hypersomnia – Kleine-Levin syndrome**

The Kleine-Levin syndrome is characterized by a pattern of unusual intermittent symptoms in subjects who appear normal between symptomatic episodes [5,10]. The core feature is periodic hypersomnia with prolonged episodes of sleep or profound stupor that may dramatically reduce wakefulness during a symptomatic day. The duration of episodes varies between a few days to several weeks. The symptom-free interval between episodes is also variable, from 1–2 months up to a year [5].

The diagnostic criteria are rather loose. Besides recurrent hypersomnia, there needs to be behavioral or cognitive symptoms in association [5]. These can vary from general “irritability” to derealization or feelings of “unreality” with confusion and hallucinations. Although often cited as the most pathognomonic features, behavioral abnormalities such as megaphagia and hypersexuality are probably relatively rare and perhaps overemphasized.

### **Behaviorally induced insufficient sleep syndrome**

Behaviorally induced insufficient sleep syndrome (BIIS) is an important differential diagnostic possibility, especially in younger people with

daytime sleepiness [19,20]. Habitual self-imposed sleep restriction can be difficult to recognize, especially in subjects who generally require more sleep than average. Sleep need does vary between people and some may require more than 8 hours per night. Relative sleep deprivation is a likely possibility when there is a tendency to extend the sleep periods during weekends or vacations. If daytime sleepiness disappears when the sleep period is extended (e.g. during holidays), BIIS is the most likely diagnosis. Chronic sleep deprivation may also result in other symptoms such as irritability, concentration problems, restlessness, or dysphoria. These symptoms may sometimes even be more pronounced than daytime sleepiness, and create diagnostic confusion, especially in adolescents.

## **Diagnostic procedures**

### **General**

Questionnaires such as the Epworth Sleepiness Scale may confirm or even pick up hypersomnia of central origin but a detailed history remains the most important tool. As outlined previously, the pattern and nature of sleepiness may point to a specific diagnosis. Additional symptoms may have important diagnostic value, such as the presence of cataplexy or REM sleep-related phenomena. Nocturnal polysomnography is used to rule out secondary forms of hypersomnia. The most assessment tool for sleepiness remains the Multiple Sleep Latency Test (MSLT, see chapter 3). It is used to confirm objectively a suspicion of hypersomnia and may also give clues to a specific diagnosis (e.g. multiple sleep-onset REM periods in narcolepsy). Sleep logs are useful in the diagnosis of BIIS, and when in doubt, actigraphy can be used as an objective assessment of habitual sleep time. Other laboratory tests have a limited place in the diagnosis of selected disorders. Neuroimaging is indicated when a secondary hypersomnia is suspected.

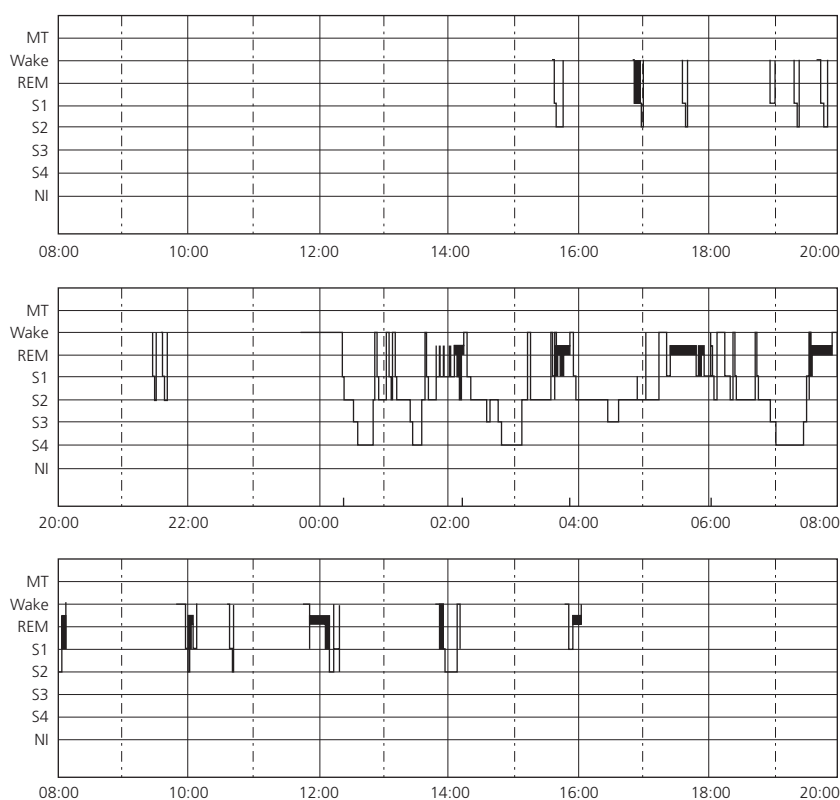
### **Narcolepsy**

Figure 19.1 shows a flowchart for the diagnostic process when narcolepsy is suspected. The single most important diagnostic clue is the presence of typical cataplexy which allows a confident diagnosis of narcolepsy in a patient with EDS. Given the consequences of such a diagnosis for work, driving, and possibly life-long treatment, it is usually appropriate to recommend confirmatory investigations with an MSLT or CSF hypocretin measurements. The MSLT criteria for narcolepsy are: a mean sleep latency of less than 8 minutes together with two or more sleep-onset REM periods. Note, however, that the MSLT must always be interpreted in the light of clinical findings given that both the sensitivity and specificity of the test

are significantly less than 100% (see chapter 3). In figure 19.2, a typical result of a nocturnal polysomnogram followed by an MSLT is shown in a patient with narcolepsy.

### Hypocretin measurements

The discovery that the majority of patients with narcolepsy with cataplexy are deficient for the hypothalamic neuropeptides hypocretin-1 and -2 led to the development of a new diagnostic technique. Hypocretin-1 can be measured in the cerebrospinal fluid, and values below 110 pg/ml are almost completely specific for narcolepsy with cataplexy [21]. As hypocretin-1 measurement requires a lumbar puncture, it should be used selectively. Specific indications include the presence of comorbid sleep



**Figure 19.2** Typical narcolepsy hypnogram, based on a polysomnographic recording starting at 16.00 throughout the night, followed by a Multiple Sleep Latency Test the next day. There are several spontaneous sleep episodes in the afternoon and early evening. There is a fragmented sleep pattern, with several awakenings throughout the night. The episode with stage 4 slow-wave sleep in the morning is unusual. During all episodes of the Multiple Sleep Latency Test stage 2 is reached, with a mean sleep latency of 4 minutes. In addition, there are three sleep-onset REM periods (during episodes 1, 2, and 4). Finally, there is a spontaneous nap between episode 1 and 2.



disorders such as sleep-disordered breathing (making the MSLT impossible to interpret), medication use that cannot be ceased, diagnosis in young children (no normative MSLT data), or a negative MSLT when narcolepsy is strongly suspected.

### **HLA typing**

More than 90% of patients with clear-cut cataplexy carry the HLA sub-type DQB1\*0602 [22]. However, the same holds true for 25–30% of the general Caucasian population. Moreover, in cases of diagnostic doubt (e.g. atypical cataplexy), the HLA association is much lower. Therefore, while HLA typing can be used to “complete” the diagnostic picture and define a homogenous patient population, it should not be used as a primary diagnostic tool.

### **Narcolepsy without cataplexy**

In the absence of cataplexy, the diagnostic process for narcolepsy is more complicated (see figure 19.1). In these cases, it is important to rule out other potential causes, especially insufficient sleep. A nocturnal polysomnograph is usually appropriate to rule out other sleep disorders. While a polysomnograph can show features that concord with narcolepsy such as a short REM latency and prominent fragmentation with an abnormal distribution of slow-wave sleep, these are not pathognomonic. The polysomnograph is followed by the MSLT which should confirm sleep-onset REM episodes, allowing distinction from idiopathic hypersomnia [2]. Hypocretin-1 levels in cerebrospinal fluid are most often normal in narcolepsy without cataplexy, but if they are low, the diagnosis is confirmed (figure 19.1).

### **Idiopathic hypersomnia**

Idiopathic hypersomnia with long sleep time usually presents with a typical history that suggests the diagnosis. A nocturnal polysomnogram should show a prolonged sleep period (typically at least 9 hours). Although a shortened sleep latency on the MSLT would be expected, borderline results are quite common (see also chapter 3). The absence of REM onset sleep periods in the MSLT is important in distinguishing idiopathic hypersomnia without long sleep time from narcolepsy without cataplexy (see above). In suspected idiopathic hypersomnia, it is important to rule out other diagnoses, for example, mood disorders which may have a higher prevalence.

### **Hypersomnia due to medical conditions**

To confirm EDS objectively, perhaps prior to treatment, the MSLT can be useful although there are no clear diagnostic cut-offs or thresholds.

Furthermore, in some syndromes, the MSLT may be difficult to perform properly due to cognitive or behavioral disturbances. Neuroimaging should be considered in atypical cases or if hypothalamic pathology, in particular, is suspected.

### **Recurrent hypersomnia – Kleine-Levin syndrome**

The diagnosis of Kleine-Levin syndrome is essentially based on a characteristic clinical picture. Between symptomatic episodes, the sleep-wake cycle is normal. The MSLT may be abnormal during an episode, but it is often difficult to perform due to a lack of collaboration from the patient. EEG studies often show a general slowing of background activity that may indicate encephalopathy but the findings are generally nonspecific.

### **Behaviorally induced insufficient sleep**

When BIIS is suspected, it can be confirmed using a patient-completed sleep diary covering at least 2 weeks. However, it is also recommended to measure the habitual sleep period objectively using actigraphy for a similar period. At a practical level, the diagnosis is confirmed when extension of the nocturnal sleep period results in resolution of daytime symptoms.

## **Management**

### **General aspects of treatment**

Behavioral advice forms the starting point for the treatment of all hypersomnias of central origin [23,24]. It is important for patients to try and keep a sleep-wake schedule that is as regular as possible. Often, scheduled daytime naps may be of benefit particularly for narcolepsy and idiopathic hypersomnia without long sleep time [25]. Planned naps of 10–20 minutes up to two or three times a day may be restorative in some patients. Longer naps may interfere with nocturnal sleep, however. Some patients benefit from avoiding carbohydrate-rich food which can exacerbate sleepiness.

Behavioral approaches are rarely sufficient for satisfactory symptom control and pharmacotherapy is needed [23,24]. The various stimulant medications that are available are discussed in chapter 6. The current “mainstay” drugs are modafinil and amphetamine-like agents such as methylphenidate or dexamfetamine itself. In general, the treatment guidelines for narcolepsy can be applied to all hypersomnias with a presumed central cause and a pragmatic approach is recommended.

In most central hypersomnias, the goal is to improve daytime functioning of a patient. The disabling effects of EDS should not be underestimated, and focussed effort on improving sleepiness is invariably appropriate. However, one should not expect to completely eliminate

symptoms of excessive sleepiness, and this should clearly be communicated with the patient.

### **Narcolepsy**

Short daytime naps can be very helpful and restorative in a significant proportion of patients. Pharmacotherapy for EDS should be tailored towards the individual patient. For most patients, modafinil is the first-line agent, especially as it provides a background level of increased alertness and has few side effects [26]. If it is not tolerated or better control is needed, traditional psychostimulants can be used instead or in addition to modafinil. These drugs are generally short-acting and can be used “on demand” for dips in alertness. Other options are discussed in chapter 6.

Although cataplexy and hypnagogic hallucinations may improve if daytime wakefulness is increased, they are usually treated separately, and several treatment options are available. Classically, these symptoms are treated with antidepressant medications [24]. The most potent drugs are probably the tricyclic antidepressants. In mild cases, these are often efficacious in very low doses (e.g. 10 mg clomipramine), so side effects are rarely problematic. Selective serotonin reuptake inhibitors (SSRIs) have been used as well to good effect but often need to be dosed somewhat higher. On theoretical grounds, combined serotonin/norepinephrine reuptake inhibitors (such as venlafaxine) are attractive and have become popular options although controlled data are lacking.

Recently, sodium oxybate (gamma-hydroxybutyrate) has become available for the treatment of narcolepsy. Because of the large body of good-quality randomized trial evidence, it has quickly grown into a first-line treatment for severe cataplexy in many countries [27]. It is a potent hypnotic with a short half-life, usually taken in two doses through the night. Besides improving night-time sleep quality, probably by enhancing the slow-wave component, sodium oxybate is also very efficacious for cataplexy. The precise mechanism is unknown and the anti-cataplectic effects appear to build over a few weeks. Treatment with sodium oxybate should only be instituted by physicians familiar with the drug and the issues around its prescription.

The disturbed nocturnal sleep in narcolepsy can sometimes be very troublesome. Classical hypnotics have limited effect and tolerance is common. Moreover, they tend to produce unrefreshing sleep. Sodium oxybate, on the other hand, improves the quality of sleep in the majority of subjects.

The leading hypothesis explaining the pathophysiology of narcolepsy states that hypocretin neurons degenerate through a monophasic autoimmune mechanism. This theory is mainly fueled by the strong HLA association but remains unproven. A few case reports have been

published in which immunomodulatory treatment – mainly intravenous immunoglobulins – was given in children with narcolepsy, shortly after disease onset. After initial very positive reports, several cases were published in which there was no long-term effect [22]. Therefore, immunosuppressant drugs do not have an established place in the treatment of narcolepsy, except in a clinical trial setting.

### **Other hypersomnias**

Idiopathic hypersomnias and hypersomnias due to a medical condition are all treated symptomatically with stimulants although no specific therapeutic trials are available. Several authors have indicated that idiopathic hypersomnia with long sleep time is relatively difficult to treat, with a less obvious response to traditional stimulants or modafinil. Higher doses than usual may often be required and specialist advice is appropriate. It is not clear whether sodium oxybate may help daytime sleepiness in non-narcoleptic populations although there is preliminary evidence that it may be helpful in sleepy parkinsonian patients [28].

### **Recurrent hypersomnia – Kleine-Levin syndrome**

During episodes, one may attempt to treat EDS with stimulants, although response seems rather limited or variable and relatively high doses may be necessary. However, stimulants do not seem to influence associated cognitive and behavioral problems. A host of different compounds have been tried to decrease the frequency of episodes, including various anti-convulsants. Lithium is the only drug that has been shown to have this effect in multiple cases, and is therefore regarded by most to be the medication of choice when treatment is considered appropriate [5,29].

### **Behaviorally induced insufficient sleep**

If BIIS is diagnosed, patients should simply extend their time in bed gradually until symptoms resolve. Pharmacological treatment should not be used for hypersomnia due to BIIS.

#### **Key points**

- It is important to distinguish (excessive daytime) sleepiness from fatigue.
- A careful history is the most important diagnostic tool.
- Think of behaviorally induced insufficient sleep syndrome, especially in young people with EDS.
- Behavioral treatment can be important, with a regular sleep-wake timing and – if possible and beneficial – daytime naps.
- There should be a low threshold for medical treatment, given the important consequences of EDS in many patients.

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## CHAPTER 20

# Neuro-immunological disorders

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## Introduction

Neuro-immunological conditions are the commonest cause of physical disability in younger populations of neurological patients. Nocturnal symptoms such as pain, spasms, and nocturia undoubtedly affect many patients, especially those in advanced stages of the disease, and are capable of fueling both symptoms of insomnia and subsequent daytime sleepiness. Restless legs and periodic leg movements may also be more prevalent in demyelinating disease [1]. In addition, associated mood disorder and drug treatments including steroids and interferons might be expected to adversely affect sleep in a substantial proportion of subjects. Other factors such as significant cognitive impairment or even dementia are likely to influence sleep but knowledge is sparse. Given the protean and sometimes extensive brain pathology seen in such patients, however, it would be surprising if there were no primary disruptive effects on the sleep-wake cycle caused by direct damage to “sleep centers” or their connections. Unfortunately, as with other neurological disorders potentially disrupting sleep, systematic clinical data characterizing typical patient profiles are lacking and treatment options remain empirical.

This chapter will focus on multiple sclerosis (MS) and the similar conditions of neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM). Although fatigue is virtually a universal symptom in neuro-immune disorders, being both poorly defined and understood, this chapter will focus more on symptoms reflecting true excessive sleepiness. Particular attention will be paid to the increasing realization that some multiple sclerosis patients may develop symptoms

compatible with narcoleptic levels of sleepiness. This will be discussed in the context of recent developments in the neurobiology of sleep-wake control mechanisms in narcolepsy and the discovery that deficiency of the hypothalamic neuropeptide, hypocretin, may cause both primary and secondary forms of the syndrome.

Although Guillain-Barré syndrome (GBS) is largely a peripheral neuro-autoimmune disorder, there are consequences for sleep-wake changes in patients with severe illness, conceivably due to poorly characterized central mechanisms.

## **Multiple sclerosis**

### **Insomnia**

It is not surprising that most patients with significant multiple sclerosis are aware that they sleep badly. Only a handful of uncontrolled studies, however, have addressed sleep problems that might be specific to multiple sclerosis. Overall, it seems clear there may be no typical nocturnal sleep disorder in multiple sclerosis and particular physical symptoms caused by the illness are the major contributors to disturbing and unrefreshing sleep. Tachibana et al. [2] concluded that leg discomfort, immobility, nocturia, and medication effects were much more relevant than breathing-related disorders, including central apnea, for example. Others have tried to correlate brain changes on magnetic resonance imaging and mood disorder with poor-quality sleep [3], having found a three-fold increase in general sleep problems in multiple sclerosis ( $n = 143$ ) compared to controls. Correlations were seen both with the degree of depression in the patient group and with the presence of white matter lesions around the supplementary motor area in particular. Although not systematically investigated, the authors suggested that nocturnal spasms may have resulted from this damaged area, disrupting sleep continuity.

Increased infratentorial or brainstem pathology has been proposed to increase the likelihood of disruptive periodic limb movements in multiple sclerosis [4]. Although this was a small sample, a recent larger study with 861 patients and 649 controls has addressed the prevalence of restless legs syndrome in patients with multiple sclerosis and found a striking five-fold increased risk [1]. It was argued that significant or resistant insomnia in multiple sclerosis may be caused by restless legs syndrome in a proportion of cases. It is not clear whether this presumed secondary form of restless legs syndrome would respond to standard treatments such as dopaminergic drugs.

Significant lower brainstem demyelinating pathology might be expected to cause central sleep apnea and disturbed sleep-wake control.



In practice, this seems a very rare phenomenon although should be considered in severely disabled multiple sclerosis patients with unexplained somnolence.

The possibility of circadian rhythm disorders has been assessed in multiple sclerosis and no convincing evidence from actigraphy has been found to support this hypothesis [5].

### **Parasomnias**

There is little published data on parasomnias that appear to have been triggered by demyelinating plaques in multiple sclerosis. However, two reports of patients with multiple sclerosis convincingly demonstrate plaques in the posterolateral pontine region that are presumed to have caused the acute onset of REM sleep behavior disorder [6,7]. In one case, the parasomnia was the presenting feature of the underlying multiple sclerosis. In the other, a 51-year-old woman with established multiple sclerosis developed vigorous dream enactment supported by polysomnograph investigations.

### **Hypersomnia**

Symptoms of fatigue aside, the issue of excessive daytime somnolence in multiple sclerosis has been discussed for many years and subsequently investigated by a number of groups (e.g. [8]). Early comparisons with narcolepsy in some severely affected patients prompted the suggestion that the diseases may share a common etiological autoimmune mechanism, especially given the reported HLA-DR2 associations in both. More specifically, an autoimmune target involving the same brain structures was proposed in both diseases [8]. However, the discovery of the selective loss of hypothalamic hypocretin neurons in (primary) narcolepsy probably implies that narcolepsy coincidentally occurs in multiple sclerosis patients when multiple sclerosis plaques appear in the hypothalamic area and secondary damage occurs to the hypocretin/orexin system [9]. In favor of this interpretation, the hypocretin system is not obviously impaired in subjects with multiple sclerosis who do not exhibit narcolepsy [10].

Two case studies are presented at the end of this chapter illustrating the general concept of secondary narcolepsy in multiple sclerosis. In both, resolution of hypothalamic lesions coincided with clinical improvement of the sleep disorder. It is suggested that bilateral hypothalamic involvement is necessary to cause hypocretin deficiency. The absence of cataplexy in these recent multiple sclerosis cases might be seen as surprising given the undetectable levels of hypocretin in the cerebrospinal fluid. This contrasts with the findings of secondary narcoleptic cases associated with multiple sclerosis reported some time ago in which 9 out of the 10 multiple sclerosis patients with narcolepsy exhibited cataplexy [9]. It is unclear whether or

not these earlier cases were treated with immunosuppressants, potentially influencing the long-term clinical outcome.

One interesting interpretation is that chronic impairment of hypocretin transmission is required before the pathognomonic symptom of narcolepsy, namely cataplexy, emerges.

## **Neuromyelitis optica**

Neuromyelitis optica (NMO) can present in a similar fashion to multiple sclerosis but is at least ten times rarer and predominantly affects certain ethnic groups. It has been recognized as a distinct disorder for some time, largely based on clinical and radiological findings. In particular, neuromyelitis optica may have a slightly different pathophysiology and involve different parts of the central nervous system to typical cases of multiple sclerosis, with lesions predominantly in the spinal cord and optic nerves. Brain involvement, as seen on magnetic resonance imaging, has traditionally thought to be much less marked than in multiple sclerosis although certain areas such as the hypothalamus might be more preferentially affected. Of interest, a specific auto-antibody has recently been proposed as a pathognomonic marker for NMO, anti-aquaporin 4 (anti-AQP4) [11]. Furthermore, AQP4, a water channel protein, is preferentially expressed in hypothalamic and periaqueductal areas [12,13] in non-neuronal structures such as astrocytes and ependymocytes.

Several cases are described in the literature in which a syndrome resembling either narcolepsy or idiopathic hypersomnolence has occurred acutely in patients with neuromyelitis optica with corresponding lesions in the hypothalamus and very low hypocretin levels in cerebrospinal fluid [14–18]. Interestingly, these cases are often associated with bilateral symmetric hypothalamic lesions. Furthermore, both the EDS and hypocretin deficiency have been seen to resolve after adequate therapeutic interventions.

Other sleep-related issues in neuromyelitis optica do not seem to have been systematically studied.

## **Acute disseminated encephalomyelitis**

Extreme symptoms of drowsiness, stupor, or even coma are recognized features of acute disseminated encephalomyelitis (ADEM), at least in the early clinical phase. These acute symptoms generally resolve with general clinical improvement but several cases have been described in which severe sleepiness persists (case 3). Since von Economo's pioneering studies [19], the concept that an inflammatory central nervous system disorder could trigger long-lasting sleep-related symptoms has been accepted. In the context of acute disseminated encephalomyelitis, recent data suggest

that hypothalamic involvement and possible hypocretin deficiency may explain the persistence of somnolence. Unlike in idiopathic narcolepsy, however, these patients generally have no clear REM sleep-related symptoms and tend to sleep excessively overnight [20,21].

## **Guillain-Barré syndrome**

Guillain-Barré syndrome is generally conceived as an acute autoimmune polyradiculopathy with a wide spectrum of severity. Respiratory failure and/or severe autonomic involvement can lead to prolonged intensive care for the patient. Although Guillain-Barré syndrome is generally restricted to the peripheral nervous system, both clinically and pathologically, clues exist that there may be central involvement [22]. These include hyponatremia caused by abnormal antidiuretic hormone (ADH) secretion [23], cases of REM sleep behavior disorder, and abnormally low hypocretin levels in cerebrospinal fluid [24]. A subset of Miller-Fisher syndrome subjects, but not subjects with chronic inflammatory demyelinating polyneuropathy (CIDP), also had significantly low hypocretin-1 in cerebrospinal fluid [24]. Subtle hypothalamic pathology in the absence of magnetic resonance imaging changes may explain sleep, hypocretin, and ADH abnormalities in this subgroup. Interestingly, all those patients with Guillain-Barré syndrome who had low hypocretin levels ( $n = 7$ ) were severe cases with profound tetraplegia, bulbar symptoms, and/or respiratory failure. The hypocretin deficiency appeared reversible in some cases, while it persisted in others [24]. Since autopsy immunostaining of hypocretin neurons has not been performed in hypocretin-deficient Guillain-Barré syndrome, it is not known whether there is actual neuronal loss in chronic cases.

It is possible that the high levels of nonspecific antibodies in the cerebrospinal fluid of some of the patients with Guillain-Barré syndrome may have neutralized hypocretin, causing a functional deficiency. Some commentators have suggested that the environment may also have contributed to the severe sleep-wake disturbance, given that it is difficult for a conscious patient to maintain a regular sleep cycle in an intensive care setting.

In general, the occurrence of sleep abnormalities in Guillain-Barré syndrome, especially in severe cases, has hitherto received little attention. The sleep latencies of two hypocretin-deficient Japanese subjects with Guillain-Barré syndrome, who complained of sleepiness after recovery from Guillain-Barré neurological symptoms, were significantly shortened (less than 1 min) in both cases [24]. However, this finding was not confirmed in white patients [25]. In another study, hypocretin concentrations were low but within the normal range in those patients with Guillain-Barré syndrome who had hypnagogic hallucinations and severely disturbed sleep, particularly the REM sleep elements as in narcolepsy [22].

## Treatment

Although largely uncharacterized in any systematic fashion, patients with multiple sclerosis and related neuro-autoimmune disorders frequently have significant sleep-wake symptoms that almost certainly adversely affect quality of life for both patients and carers. Wherever possible, disruptive nocturnal symptoms that might be acting as sleep “toxins” should be actively addressed. If (neuropathic) pain and sleep fragmentation are major symptoms, a variety of agents can be considered although controlled evidence for efficacy is lacking. Antidepressants are commonly used, often with the implicit hope that any associated depressed mood will also improve. If there is additional potentially troublesome nocturia, for example, a sedating tricyclic agent such as amitriptyline to help bladder control and improve pain might be a sensible option. Although sleep quantity may improve with this approach, overall sleep quality can deteriorate and motor phenomena such as periodic limb movements might become disruptive.

Alternative neuropathic pain agents may improve sleep quality more effectively by enhancing the non-REM slow-wave component. These include pregabalin (150–300 mg/day) and gabapentin (300–1800 mg/day).

Nocturnal spasms are often also a disturbing influence to sleep continuity and muscle relaxants such as baclofen (10–90 mg/day) or even botulinum toxin may directly improve sleep quality.

There have been small trials assessing a variety of stimulants to improve daytime alertness in patients with multiple sclerosis. However, it is not always clear whether these have addressed fatigue or sleepiness *per se*. Amantadine (100–300 mg/day) or selegiline (2.5–20 mg/day) are traditionally used and there is limited published evidence for efficacy, at least for fatigue [26]. However, in practice, positive responses to these drugs are unpredictable. After initial reports of promising effects, the wake-promoting agent modafinil at a reasonable dose of 400 mg did not appear to improve fatigue in a controlled study assessing 115 patients [27]. Individual patients, however, often report great benefit.

In patients with multiple sclerosis who are clearly hypersomnolent, potentially due to central nervous system inflammatory pathology directly affecting areas regulating the sleep-wake cycle, conventional treatments for narcolepsy appear entirely reasonable. Modafinil with or without additional psychostimulants such as dexamphetamine (5–20 mg/day) or methylphenidate (10–60 mg/day) may be hoped to improve wakefulness in those with a narcoleptic phenotype. As illustrated in the cases presented, if hypersomnolence develops in the context of an

acute multiple sclerosis relapse, immunosuppression with steroids appears to help or at least coincide with symptom improvement. This may imply that edema surrounding an inflammatory plaque near the hypothalamus, for example, is primarily responsible for disrupting the sleep regulatory pathways.

Motor disturbances at night in multiple sclerosis should be treated empirically. Clonazepam (0.5–4 mg/day) appears effective if REM sleep behavior disorder is present [7], and is also likely to improve other parasomnia-like activity, if present. It is not known whether dopaminergic agents or opioids improve restless legs syndrome and periodic limb movements when secondary to multiple sclerosis pathology. However, in other causes of secondary restless legs syndrome such as uremia, these drugs appear effective and would therefore be worth trying.

## **Conclusions**

Sleep-related symptoms may well be overlooked in patients with neurological problems secondary to autoimmune disease with focus directed primarily on the potentially disabling physical sequelae. However, as with many other chronic neurological illnesses, the sleep-wake cycle can be profoundly affected in a variety of ways with adverse consequences affecting quality of life.

In multiple sclerosis, for example, most treatments remain “symptomatic” rather than disease-modifying. If sleep-related problems are revealed, any such treatments should be tailored to improve sleep quantity and, importantly, its overall quality.

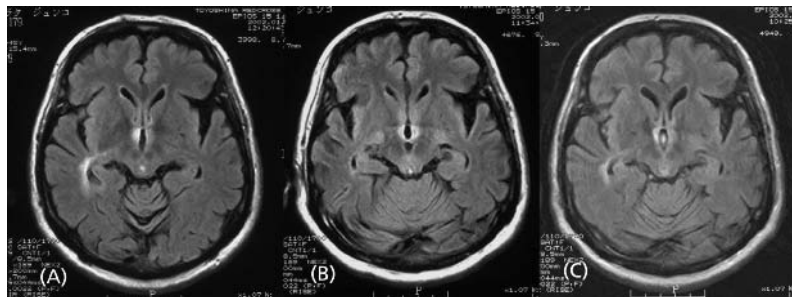
The drug treatment of fatigue is often disappointing in neurological patients with inflammatory pathology. However, it is increasingly realized that a subset of patients have true excessive somnolence and exhibit symptom profiles highly suggestive of secondary narcolepsy. Intriguingly, with recent advances in understanding the neurobiological basis of idiopathic narcolepsy, many of these subjects will have inflammatory lesions bilaterally in the hypothalamic region to cause the sleep-wake disturbance. Recent developments in neuromyelitis optica and defining the role of anti-AQP4 antibodies suggest that this condition may be particularly at risk of narcoleptic symptomology. Lesions often appear reversible, possible with immunosuppressive therapy, emphasizing the importance of early therapeutic interventions. However, persisting symptoms of somnolence merit treatment with standard stimulant drugs.

### Key points

- Sleep-related symptoms are almost certainly very common in conditions such as multiple sclerosis although they remain poorly characterized.
- Insomnia is probably the commonest consequence and is usually secondary to physical symptoms such as pain, spasms, and nocturia.
- Restless legs syndrome may be much commoner in multiple sclerosis patient populations. It is not clear whether it responds to standard restless legs syndrome treatment strategies.
- In demyelinating conditions such as multiple sclerosis, fatigue is extremely prevalent. Only a proportion of such patients suffer true hypersomnolence.
- A form of secondary narcolepsy has been well described in multiple sclerosis and neuromyelitis optica, almost certainly arising from damage to the hypocretin system. In some cases this appears reversible. Guillain-Barré syndrome also affects the sleep-wake cycle in severe cases with particular abnormalities of REM sleep reported.

### Case 1

A 45-year-old female developed striking hypersomnia during a multiple sclerosis relapse (figure 20.1). Initially, 5 days before admission, she experienced “sleep attacks” while cooking and conversing. She then became generally excessively drowsy. The left panel of figure 20.1 shows a brain magnetic resonance image taken half a month before the occurrence of hypersomnia, with a hypothalamic lesion only on the right side. After admission, magnetic resonance imaging revealed a new lesion in the left hypothalamus. The hypocretin level in cerebrospinal fluid was below 40 pg/ml (<110 pg/ml is diagnostic for narcolepsy).



**Figure 20.1** A 45-year-old female patient with multiple sclerosis, with hypersomnia and undetectable orexin level (<40 pg/ml) [28]. The image on the left was taken half a month before the occurrence of hypersomnia. There was only right hypothalamic lesion. The central panel was on the 3rd hospital day. The patient was suffering from hypersomnia at this time. There was a newly occurred lesion of left hypothalamus. The image in the right panel was taken on the 32nd hospital day when hypersomnia had already subsided. It is noteworthy that the left hypothalamic lesion has disappeared. From this case, it appears that bilateral lesions are needed for the symptom of hypersomnia.

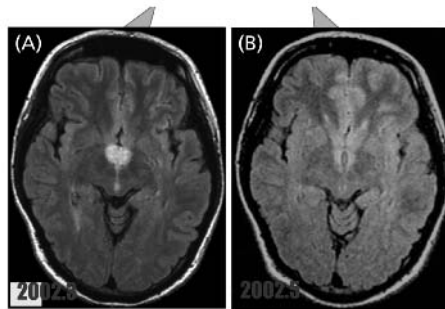
Methylprednisolone pulse treatment was started followed by oral prednisolone. Three days after the initiation of methylprednisolone, the patient's hypersomnia completely resolved. Twenty days later, hypocretin levels recovered to 167 pg/ml.

The right panel of figure 20.1 is an image of the patient's brain taken after 32 days of hospitalization following subsidence of the hypersomnia. It is noteworthy that the left hypothalamic lesion has disappeared. A causal relationship between bilateral hypothalamic pathology, hypersomnia, and decreased hypocretin level has been suggested [28].

## Case 2

A 22-year-old female with multiple sclerosis presented with severe hypersomnia. Her nocturnal sleep time was prolonged at 15 hours and a subsequent mean sleep latency was 2.8 minutes. The REM sleep latency during the MSLT was less than 5 minutes with REM onset in all five nap opportunities. However, she did not experience clinical cataplexy, hypnagogic hallucination, or sleep paralysis. Her HLA type was DR4 and DR6. A brain magnetic resonance scan revealed hyperintensity in the hypothalamus bilaterally on the FLAIR images (figure 20.2A) and CSF hypocretin levels were undetectable (< 40 pg/ml).

	11 days	2 months	4 months
<b>Multiple Sleep Latency Test</b>			
<b>Mean Sleep Latency</b>	2.8	17.4	14.8
<b>Number of SOREMPs / Naps</b>	5/5	1/5	0/5
<b>Mean REM Latency</b>	4.7	8.5	-
<b>CSF hypocretin-1 (pg/ml)</b>	<40	167	232



**Figure 20.2** A 22-year-old female patient with bilateral hypothalamic lesions of multiple sclerosis. Her nocturnal sleep time was 15 h, sleep latency by MSLT was 2.8 min, and REM latency was 4.7 min with 5 SOREMPs. Her HLA was DR2 negative and an MRI revealed FLAIR hyperintensity in the hypothalamus bilaterally. (A) Axial section of FLAIR image. Bilateral hypothalamic plaque is demonstrated as a median high intensity area. (B) The plaque disappeared 1 month later with steroid treatments.

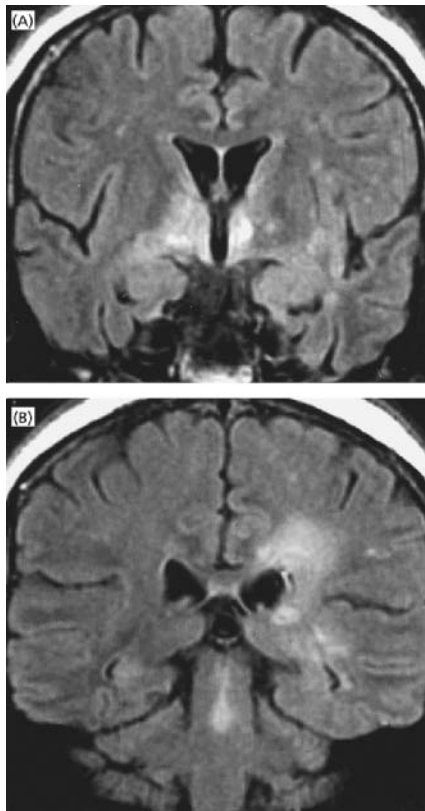
(continued)

After intravenous methylprednisolone and subsequent oral prednisolone, her symptoms resolved. On a second evaluation 2 months later, the patient had no symptoms of hypersomnia and her hypothalamic MR appearances were diminished (figure 20.2B). MSLT now revealed a normal mean sleep latency of 17.4 minutes and REM sleep appeared only once. Repeat CSF hypocretin levels were 177 pg/ml. On a third evaluation 4 months later CSF hypocretin levels were within the normal range (211 pg/ml).

It is suggested that reversible bilateral hypothalamic lesions due to demyelination caused transient severe hypersomnolence with sleep investigations and hypocretin levels consistent with a diagnosis of (secondary) narcolepsy. The documented episodes of sudden REM onset are particularly interesting [29].

### Case 3

Gledhill et al. [30] reported a 38-year-old female with acute disseminated encephalomyelitis (ADEM) and severe hypersomnia. She had no REM-related symptoms such as cataplexy, hypnagogic hallucinations, or sleep paralysis. Brain magnetic resonance imaging revealed lesions in the hypothalamus, walls of the third ventricle, corona radiata, floor of the aqueduct, and raphe nuclei (figure 20.3). Her HLA type was positive for DR2/DQB1\*0602 and her hypocretin-1 levels were low at 87 pg/ml. She was treated with high dose steroids.



**Figure 20.3** A 38-year-old female patient with severe EDS and internuclear ophthalmoplegia. MSLT results demonstrated short sleep latencies and 4 SOREMPs. MRI showed T2 and fluid attenuated inversion recovery hyperintensity along the walls of the third ventricle (A) and in the corona radiata, floor of the aqueduct, and raphe nuclei (B), which are consistent with acute disseminated encephalomyelitis. After treatment with steroids, this patient's subjective sleepiness, hypersomnia, and hypocretin deficiency partially improved [30].



A subsequent MRI scan showed smaller and fewer lesions. Six months later, her subjective sleepiness was partially improved. At this point, her mean sleep latency on the MSLT (four naps) was 4.4 minutes with REM sleep recorded in all nap opportunities. Her hypocretin levels had improved to 148 pg/ml.

One year after her initial examination, her sleepiness persisted and the results of MSLT were almost unchanged.

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## CHAPTER 21

# Tumors and paraneoplastic syndromes

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In this chapter the sleep-wake disturbances occurring in patients with tumors both outside and within the central nervous system are reviewed, including indirect or paraneoplastic effects.

### **Sleep in patients with systemic tumors**

Patients with systemic neoplasms outside the central nervous system frequently report a variety of sleep disturbances which include insomnia, excessive daytime sleepiness (EDS), fatigue, and disruption of the sleep-wake cycle. Insomnia is common both in subjects with a recent diagnosis of cancer, usually secondary to anxiety and depression, and in those with advanced disease. Fatigue is particularly frequent during chemotherapy sessions but may occur in any stage of the disease [1,2].

As with most severe chronic illnesses, sleep-related symptoms may contribute significantly to quality of life issues in patients with cancer and their carers. Nonrestorative sleep may interfere not only with patients' activities of daily living but may also affect their attitude and ability to face the disease and its treatment. However, patients with cancer generally do not spontaneously report their sleep disturbances to oncologists, often because they feel they are intrinsic to the underlying problem and would be difficult to resolve. Given that most physicians do not routinely ask about sleep proactively, disturbances often remain unrecognized and thereby untreated.

### **Sleep in patients with cancer**

Over the last decade several studies have assessed the quality of sleep in patients with cancer and its impact on quality of life. The majority of

published studies are descriptive, evaluating sleep with subjective scales and questionnaires. Studies using polysomnography are scarce. Overall, studies have shown that sleep quality is frequently poor among both newly diagnosed and advanced patients with cancer. Poor sleep quality in patients with cancer may relate to general health-related quality of life problems, anxiety, depression, pain, nausea and vomiting, or difficulty in turning in bed. It can be worsened by medications including chemotherapy and opioids for pain relief. In addition, during the course of the disease, patients may develop primary sleep disorders such as sleep apnea due to upper airway obstruction, especially in head and neck cancers, or restless legs syndrome perhaps secondary to iron deficiency anemia, seen particularly in gastrointestinal carcinomas.

A cross-sectional survey in 982 patients examined the prevalence and characteristics of reported sleep problems in patients attending six clinics at a regional cancer center [3]. Patients were attending clinics for breast, gastrointestinal, genitourinary, gynecological, lung, and non-melanoma skin cancers and were offered a brief sleep questionnaire. The most prevalent sleep problems were excessive fatigue (44%), leg restlessness (41%), insomnia (31%), and EDS (28%). Recent cancer treatment with chemotherapy was associated with excessive fatigue and hypersomnolence. Insomnia commonly involved multiple awakenings. In 48% of cases, insomnia onset was reported to occur around the time of cancer diagnosis. The most frequently identified contributors to insomnia were thoughts, concerns, and pain or discomfort.

Few studies have evaluated sleep architecture in patients with systemic cancer. Polysomnography usually shows that patients with lung cancer have long sleep-onset latency, low sleep efficiency, and high wake time after sleep onset when compared with controls. In a study, 114 patients with advanced solid tumors underwent ambulatory polysomnography for 42 hours in their home. Patients had reduced quantity and quality of nocturnal sleep and episodes of sleep scattered throughout the day. Increased daytime sleep was negatively associated with several parameters of nocturnal sleep quantity and quality [4].

### **Treatment of sleep disturbances in patients with systemic cancer**

Treatment should always be individualized. Sleep hygiene and attempts to restore the integrity of the sleep-wake cycle by physical activity or psychotherapy are often worthwhile. The use of sedating antidepressants (e.g. mirtazapine and trazodone) may improve sleep quality in patients with depression. Short-acting benzodiazepines such as lorazepam may improve sleep-onset insomnia when anxiety appears to be the cause. Long-acting opioids such as morphine and transdermal fentanyl may improve

nocturnal pain. Sleepiness and even fatigue may respond to central nervous system stimulants, an option that is frequently overlooked.

## **Sleep in patients with brain tumors**

Clearly, patients with neoplasms of the central nervous system develop neurological symptoms depending on the structures that are damaged. Lesions may variably result from the tumor load itself, any surrounding edema, resective surgery, and cranial radiotherapy. Not surprisingly, a variety of sleep disturbances may develop in patients with brain tumors, particularly EDS. However, the full range of sleep disorders have also been described, including REM sleep behavior disorder, central sleep apnea, insomnia, seizures during sleep, sleep-related eating syndrome, and confusional arousals. The posterior hypothalamus and rostral brainstem are the two most common locations where tumors may directly cause sleep-wake disruption. The main sleep disturbances associated with brain tumors are reviewed below.

### **Symptomatic narcolepsy**

Idiopathic narcolepsy is a sporadic disease characterized by EDS, cataplexy, sleep-onset REM periods in the MSLT, positivity for HLA-DQB1\*0602, and undetectable CSF hypocretin-1 concentrations (see chapter 19). Excessive daytime sleepiness combined with other narcoleptic features can occur in the setting of several other conditions and is generally known as “symptomatic” or “secondary” narcolepsy. Brain tumors are one of the most frequent causes of symptomatic narcolepsy, occurring in 29% of reported cases [5]. However, it is a rare condition with no more than 50 examples reported in the medical literature (a detailed review of 33 cases was published in 2005 [5]). The most frequent location (70%) for a tumor to produce symptomatic narcolepsy is the hypothalamus or its adjacent structures such as the pituitary gland, suprasellar region, third ventricle, and pineal gland. In these patients, other symptoms related to general hypothalamic damage are common such as obesity, diabetes insipidus, and panhypopituitarism. In patients with symptomatic narcolepsy, dysfunction of the hypocretin system is highly suspected when neoplasms extend to the posterior hypothalamus. Other cases of symptomatic narcolepsy involve the upper brainstem (9%), multiple brain areas (9%), cerebellum (6%), temporal lobe (3%), and frontal lobe (3%). Some tumors causing secondary narcolepsy predominantly affect children (e.g. craniopharyngioma, medulloblastoma) while others mainly affect adults (e.g. glioblastoma, lymphoma).

Patients with brain tumors and secondary narcolepsy always have EDS which in some cases may be the presenting symptom and is usually one

of the most disabling. In other patients, EDS is moderate or mild. Apart from the levels of EDS, the clinical phenotype is usually different to idiopathic narcolepsy-cataplexy. Cataplexy frequently is absent and the association with HLA-DQB1\*0602 is not strong. Early-onset REM sleep episodes may not be shown in the Multiple Sleep Latency Test and low levels of hypocretin-1 may not be detected in the cerebrospinal fluid [5]. It remains unknown which factor or combination of factors determine the narcoleptic phenotype in patients with a brain tumor. The severity and nature of damage to the hypocretin system is likely to be important as is the location, size, and nature of the tumor, together with any predisposing immune or genetic factors.

Of the symptomatic narcolepsy cases secondary to brain tumors, 55% exhibit cataplexy [5]. Sleep paralysis and hypnologic hallucinations may occur in some patients with brain tumors located in the brainstem and hypothalamus [6].

Nocturnal polysomnography followed by MSLT has been performed in a few patients with symptomatic narcolepsy due to brain tumors [5]. As in idiopathic narcolepsy, the MSLT may show two or more REM sleep onset periods in most of the patients, but polysomnography does not usually show reduced REM sleep latency [5].

Hypocretin-1 levels in cerebrospinal fluid have been evaluated in only a few subjects with brain tumors and symptomatic narcolepsy [5,7,8]. Undetectable, low (<110 pg/ml), intermediate (110–200 pg/ml), or normal (>200 pg/ml) levels have all been reported. In subjects with reduced hypocretin-1 level in the cerebrospinal fluid, severe damage either in the hypocretin-producing neurons in the posterior hypothalamus or in the hypocretin projections are thought to occur. Interestingly, it has been reported that effective treatment of a brain tumor was associated with normalization of the CSF hypocretin-1 level in a patient with previously undetectable value [7].

### **Treatment of symptomatic narcolepsy**

Hypersomnolence associated with brain tumors may respond to central nervous system stimulants [9]. In some cases, effective treatment of the tumor may result in improvement of the narcoleptic features in conjunction with other neurological symptoms such as visual field defects, oculomotor abnormalities, and motor weakness. Normalization of hypocretin-1 levels in the cerebrospinal fluid may also occur [7]. In contrast, disabling hypersomnolence following tumor removal may persist, especially in children [10].

### **Excessive daytime sleepiness without narcoleptic features**

Some patients with brain tumors develop significant but non-narcoleptic levels of EDS in the absence of cataplexy. In such cases, although

hypocretin-1 levels are generally normal within cerebrospinal fluid, mild but critical dysfunction of hypocretin neurotransmission cannot be excluded. Tumors are often located in non-hypothalamic structures involved in sleep-wake cycle regulation such as the thalamus [5].

In some tumors damaging the hypothalamus, weight gain may lead to obstructive sleep apnea and hypersomnolence. However, particularly in children, successful treatment of obstructive sleep apnea in the context of hypothalamic and brainstem tumors rarely resolves the hypersomnolence [10]. Transient or permanent EDS can also occur after several weeks of cranial radiation in patients with brain tumors [10].

### **Isolated symptomatic cataplexy**

A few adult cases of symptomatic cataplexy not linked to EDS have been reported in the literature. Interestingly, isolated symptomatic cataplexy is not necessarily associated with tumors located in the hypothalamus [5]. Although direct damage of the hypocretin cells in the hypothalamus seems unlikely in many cases, damage to structures receiving hypocretin projections from the posterior hypothalamus cannot be excluded. A temporal association between cataplexy onset and meningiomas located in the frontal and parietal lobe was reported in five adults aged 50–68 years [11]. Other examples include a 6-year-old girl with a pontomedullary pilocytic astrocytoma who developed isolated cataplexy [12] whereas an adult with glioblastoma of the hypothalamus and upper brainstem developed continuous cataplectic attacks and sleep paralysis [13].

### **REM sleep behavior disorder**

A few human cases have been reported with REM sleep behavior disorder (RBD) secondary to a focal lesion in the brainstem and/or limbic areas such as the amygdala. The variable nature of these lesions may be inflammatory, vascular or tumoral [14]. To the best of our knowledge there are no more than ten cases published in the medical literature of RBD secondary to brain tumors. In these published reports, tumors are located in the brainstem or in the pontocerebellar angle [15,16]. A 59-year-old man with a neurinoma of the left pontocerebellar angle developed deafness of the left side over a period of 6 years and RBD symptoms with unpleasant dream enactment over a period of 5 years. REM sleep behavior disorder was confirmed by polysomnography and symptoms were successfully treated with clonazepam, the treatment of choice for RBD. REM sleep behavior disorder symptoms disappeared after the tumor was surgically removed, allowing discontinuation of clonazepam. The authors postulated that the tumor interfered with the brainstem circuitry responsible for REM sleep atonia [15]. In abstract form, two cerebellopontine angle meningiomas and one

petrous ridge meningioma were reported to occur in three adults with RBD. In one case resection of the meningioma led to resolution of RBD symptoms [16].

## **Disordered sleep in paraneoplastic syndromes**

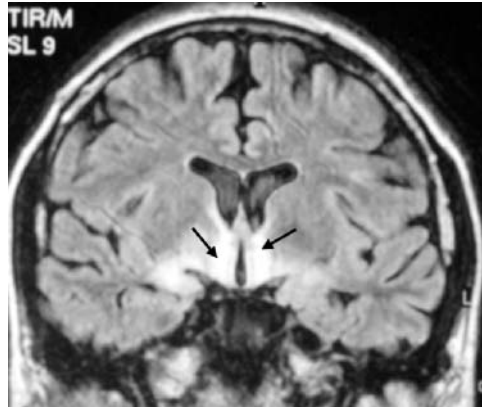
### **Excessive sleepiness**

Paraneoplastic neurological syndromes (PNS) are disorders related to neoplasms outside the nervous system and include phenomena such as limbic encephalitis and a subacute cerebellar syndrome [17]. By definition, PNS are not caused by metastases or infiltration of a tumor in the brain, but are generally immune mediated and linked to cross-reacting onconeural antibodies against neural antigens expressed by the tumor and the nervous system. In most PNS, the direct pathogenic role of the antibodies is unknown however. Autopsy shows neuronal loss, gliosis, and inflammatory infiltrates of cytotoxic T-lymphocytes. Importantly, PNS often precedes the diagnosis of the underlying systemic malignancy. Paraneoplastic neurological syndromes are relatively common in patients with lung, ovary, breast, and testicular cancer and Hodgkin disease. The clinical course is usually subacute and progressive. Symptomatology can be severe and may involve any area of the nervous system. Patterns of neurological dysfunction depend on the brain structures where the antigens are prominently expressed in the brain. Common sites include dorsal root ganglia, cerebellum, amygdala, hippocampus, brainstem, hypothalamus, and thalamus [17].

Sleep disorders in patients with PNS have received attention only recently and prospective, well-designed studies have not been published. Indeed, only small series and case reports have described patients with PNS suffering from sleep disturbances such as EDS, REM sleep behavior disorder, and central respiratory abnormalities. In most of the reported cases, sleep studies were not performed and hypocretin-1 level in cerebrospinal fluid was not measured. The severity of sleep problems in patients with PNS ranges from mild to severe and such symptoms may be overshadowed by other manifestations of the PNS. In particular, associated damage to limbic, brainstem, or diencephalic structures may dominate the clinical picture.

Hypersomnia has most often been described in patients with anti-Ma2 encephalitis linked to testicular and lung tumors. The resulting PNS affects diencephalic, limbic, and brainstem structures in any combination (figure 21.1). Several cases have been reported with variable degrees of additional sleep tests (table 21.1). In a detailed review of 38 cases with anti-Ma2-associated encephalitis published in 2004, the authors





**Figure 21.1** Coronal FLAIR MRI showing high signal in the hypothalamus and amygdala (see arrows to the hypothalamus) in a patient with anti-Ma2 encephalitis and testicular germinoma who presented with hypersomnia.

noted that “EDS affected 32% of the patients, sometimes with narcolepsy-cataplexy and low CSF hypocretin” [18]. Of the 13 patients that developed hypothalamic dysfunction with weight gain, hyperthermia, diabetes insipidus, gelastic seizures, 12 had EDS and two of them presented a narcoleptic phenotype characterized by cataplexy and hypnagogic hallucinations. None of these 12 patients underwent sleep studies and hypocretin was not evaluated in the two patients with cataplexy. One of the patients without cataplexy was “lethargic and napping more than usual” and CSF hypocretin was undetectable while MRI showed abnormalities in the right thalamus, midbrain and mesial temporal lobe but not in the hypothalamus [19]. This review [18] included six patients with anti-Ma2 encephalitis previously published [20]. Cerebrospinal fluid hypocretin was undetectable in four presenting with EDS and normal in two without EDS. None of these six patients underwent sleep studies and the presence of cataplexy could not be determined because the study was retrospective. HLA haplotypes were not determined and brain MRI did not detect abnormalities in the hypothalamus. This was the first report indicating that hypocretin deficiency can have a definite autoimmune-mediated cause [20]. In another case series that involved 22 newly diagnosed patients with anti-Ma2 encephalitis, four presented with EDS but sleep studies and hypocretin status were not evaluated [21].

Central hypoventilation may be seen in patients with (1) anti-Hu brainstem encephalitis associated with small cell lung cancer and (2) anti-NMDA receptor encephalitis linked to ovarian teratoma. In contrast, sleep problems seem to be uncommon in PNS patients with (1) sensory

**Table 21.1** Studies reporting excessive daytime sleepiness in patients with paraneoplastic anti-Ma2 encephalitis

Reference	EDS (n)	Cataplexy (n)	HLA DR2	PSG (SE)	MSLT	MRI hypothalamic lesion	CSF hypocretin (pg/ml)
Overeem et al. [20]	4 of 6	Unknown	ND	ND	ND	No	Low in 2 with EDS and normal in 2 without EDS
Blumenthal et al. [19]	1	NR	ND	ND	ND	No	Undetectable
Dalmau et al. [18]	12 of 38(*)	2	ND	ND	ND	No	Low in 5 with EDS, not reported in the remaining 7 with EDS*
Hoffmann et al. [21]	4 of 22	NR	ND	ND	ND	NR	ND
Landolfi et al. [22]	1	Yes	Neg	44%	SL = 9 min SOREMP = 2	No	ND
Rojas-Marcos et al. [23]	1	No	ND	ND	ND	Yes	low
Compta et al. [24]	1	No	Neg	48%	SL = 7 min SOREMP = 4	No	low
Sahashi et al. [25]	1	NR	ND	ND	ND	Yes	ND
Bennet et al. [26]	1 of 2	NR	ND	ND	ND	Yes	ND
Waragai et al. [27]	1	NR	ND	ND	ND	No	ND

\*The report by Dalmau et al. [18] includes the patient reported by Blumenthal et al. [19] and the six patients reported by Overeem et al. [20].

CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; MSLT, Multiple Sleep Latency Test; ND, not done; NR, not reported; Neg, negative; PSG, polysomnography; SE, sleep efficiency; SL, sleep latency; SOREMP, sleep-onset REM periods.

neuronopathy due to anti-Hu antibodies against the dorsal root ganglia and (2) subacute cerebellar syndrome associated with anti-Yo antibodies against Purkinje cells.

### **REM sleep behavior disorder**

This parasomnia, confirmed by video-polysomnography, was reported in a patient with anti-Ma2 encephalitis who presented with parkinsonism among other symptoms [24]. REM sleep behavior disorder severity was mild and MRI demonstrated damage to the dorsolateral mesopontine tegmentum and bilateral amygdala. It may be speculated that in RBD limbic system dysfunction contributes to development of the characteristic frightening dreams, and brainstem dysfunction to lack of muscle atonia and dream-enacting behaviors during REM sleep.

### **Central hypoventilation**

Central hypoventilation has been described in patients with anti-Hu [28–31] and anti-NMDA-receptor encephalitis [32,33]. Of 22 patients with anti-Hu-associated pure brainstem encephalitis, central alveolar hypoventilation occurred in five, with isolated medullar involvement also exhibiting other bulbar symptoms such as dysphagia, dysphonia, and dysarthria [28–30,34]. The clinical course was rapidly progressive, requiring orotracheal intubation and mechanical ventilation at the emergency room or a few days after admission. Subacute respiratory failure was the major problem leading to admission in all cases. During wakefulness, patients exhibited dyspnea but could breathe spontaneously. By contrast, during sleep, failure of automatic respiration produced severe and prolonged central apneas, akin to “Ondine’s curse.” Underlying associated malignancies were small cell lung tumors, and renal and prostate adenocarcinomas.

Central hypoventilation also appears as a common phenomenon in young women with ovarian teratoma and anti-NMDA-receptor encephalitis. In a recent series of 100 patients with anti-NMDA-receptor encephalitis, central hypoventilation occurred in 66 [33]. Central hypoventilation is usually severe, requiring mechanical support for a few weeks or many months [33,35]. Of interest, knockout animals of NR1 subunit of the NMDA receptor tend to die of hypoventilation [36]. Patients, however, typically present with hallucinations, delusions, seizures, short-term memory loss, movement disorders, and decreased level of consciousness. Brain MRI is normal or may show abnormalities in the mesial temporal lobes, basal ganglia, and brainstem [32]. Autopsies reveal extensive microgliosis, rare T-cell infiltrates, and neuronal degeneration in the hippocampus and other regions including the brainstem [32]. Most patients recover after tumor removal and appropriate immunotherapy.

**Key points**

- Many patients with systemic tumors have sleep problems, most often characterized by disturbed nocturnal sleep and excessive daytime sleepiness.
- Sleep-onset or sleep-maintenance insomnia may be significant, contributing to disability and adversely affecting cancer treatment.
- If questioned, many patients with brain tumors report sleep-wake disturbances, especially if the posterior hypothalamus and rostral brainstem are involved.
- Over one-third of cases of symptomatic narcolepsy are associated with central nervous system tumors.
- Sleep disorders in paraneoplastic syndromes are rarely explored but symptomatic narcolepsy with anti-Ma2 antibodies, REM sleep behavior disorder, and severe nocturnal central hypoventilation (Ondine's curse) are increasingly recognized.

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## CHAPTER 22

# Effects of medication on sleep and wakefulness

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## Introduction

Sleep and wakefulness are processes governed by several partly overlapping neuroanatomical and neurochemical systems in the brain. This chapter summarizes the most important principles of sleep physiology and pharmacology, aimed at helping the clinician to understand how sleep and wakefulness are affected not only by neurological disorders but also by their medical treatment. The latter is highly relevant since impairments of sleep or wakefulness, namely insomnia or somnolence, are among the most frequently reported adverse event across the pharmacopeia. Understanding the pharmacological basis of sleep and wakefulness can both aid the clinical analysis of sleep disorders and guide choices for appropriate medication in neurological and psychiatric practice.

## Sleep and wake systems in the brain

Historically, based largely on the original and prescient clinicopathological observations of von Economo, a clear neuroanatomical distinction has been made between sleep- and wake-promoting systems. In particular, von Economo found that patients with encephalitic lesions of the anterior hypothalamus appeared to develop severe insomnia whereas, more commonly, patients with lesions in the posterior hypothalamus became excessively somnolent. This suggested that centers in the anterior hypothalamus were involved in the generation and maintenance of sleep, a notion corroborated by early animal data. Thus, cats with midpontine lesions were found to be extremely hypersomnolent. Moruzzi and Magoun subsequently proposed the existence of an ascending reticular

activating system involved in the maintenance of wakefulness. They demonstrated that stimulation of the brainstem reticular formation converted the high-voltage synchronized electroencephalographic (EEG) activity, characteristic of sleep and anesthesia, into the desynchronized low amplitude activity of waking.

Neurophysiologically, sleep has been associated with an increased inhibitory drive, especially through activation of GABA-ergic systems arising predominantly from the lateral preoptic area of the anterior hypothalamus. Indeed, the bulk of current hypnotic medication, including benzodiazepines, consists of compounds facilitating GABA-ergic transmission. By contrast, waking has been associated with an increased excitatory drive through a number of neurotransmitter systems, particularly stimulant biogenic amines (norepinephrine, dopamine, histamine, serotonin) and acetylcholine, each emanating from specific nuclei in the brainstem and posterior hypothalamus. Wake-promoting systems are essential for wakefulness although sleep may be prevented if they are too active. Consequently, agonists of these biogenic amines, used in a variety of situations, often cause insomnia, whereas antagonists are frequently associated with sedation. An increasingly held view is that insomnia is more a disorder of hyperarousal rather than one primarily of impaired sleep mechanisms. This has fueled developments in hypnotic medication and prompted a shift in emphasis from activation of sleep-inducing networks to the inhibition of arousal systems.

### **Sleep-related drug side effects**

In this chapter, the most relevant neuropharmacological systems are presented, together with the routinely used medications that can have an impact on the sleep-wake cycle. Appendix B provides an overview of several drug classes with their most important pharmacological mechanisms of action and impact on sleep or wakefulness. The overview is derived not so much from published polysomnography studies but more from descriptions rooted in clinical practice and experience. Appendix B lists many different drugs currently in use but excludes general anesthetics, locally applied medications, supplements such as enzymes, minerals or vitamins, as well as recreational or illicit drugs. It provides general information on the severity of sleep-wake effects in the clinical dose range as derived from the frequency of adverse events mentioned in the labeling information.

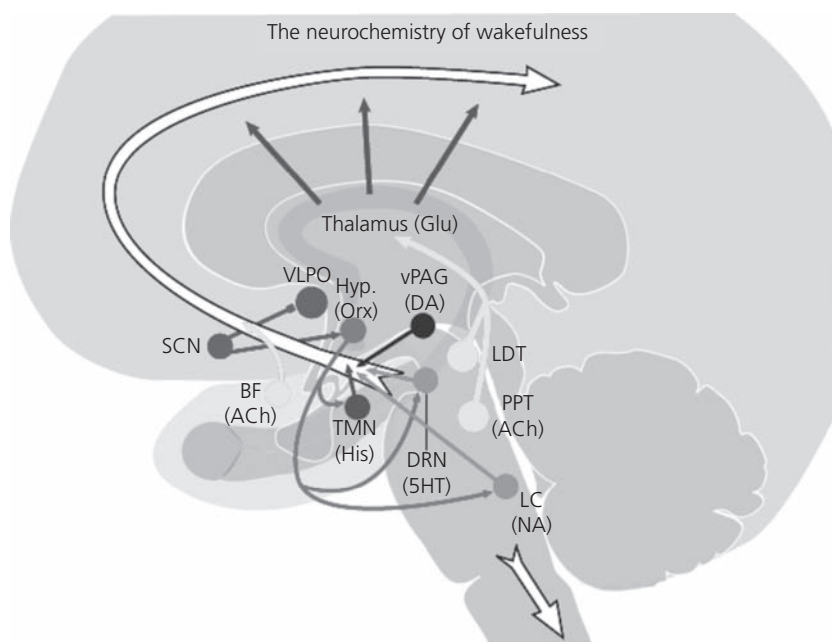
Several drug classes not generally used to treat diseases of the nervous system may still cause prominent sedation or insomnia. This can be due either to secondary pharmacological effects impacting on sleep-wake regulation, or to indirect physiological effects that affect circadian regulatory processes. The precise therapeutic indication of a drug may also have



an effect on the type of adverse event reported. Sildenafil, for instance, is used to treat both pulmonary hypertension and erectile dysfunction. Insomnia is quite frequently reported with the former indication but not with the second, related potentially not only to differences in dosing but also to the fundamental differences in the treatment conditions. It should also be noted that some drugs which might be expected to have an effect on sleep-regulatory systems, based on their profile, are not listed as having such effects in appendix B. This may be due to the limited therapeutic dose range of the drug, to inadequate blood-brain barrier penetration, or to contrasting effects on sleep and wakefulness due to the disease itself and its treatment. It should also be stressed that insomnia or sedation secondary to treatment effects may be exaggerated in some subjects due a variety of factors. These include high plasma levels as a result of reduced clearance or high doses, increased blood-brain barrier penetration in severe systemic or brain disease, or an increased sensitivity of the central nervous system in the very young or the elderly. Under these conditions, the severity or frequency of side effects of drugs with well-known effects on sleep or wakefulness may also increase, sometimes to levels of delirium, hallucinations, stupor, and even coma. An understanding of the pharmacology of the systems involved in the sleep-wake cycle can therefore also contribute to understanding impairment of consciousness. The emphasis of this chapter, however, is on excessive sleepiness, significant insomnia, and abnormal dream or nightmare activity at *therapeutic* dose levels.

## Neuropharmacology of waking and REM sleep

No single neurotransmitter system is required absolutely to keep a subject awake. Rather, wakefulness is maintained by multiple parallel arousal systems. However, the different neurotransmitter systems implicated in wakefulness, such as acetylcholine, histamine, norepinephrine, serotonin, dopamine, glutamate, and hypocretin (orexin) may mutually excite each other and, as such, act in concert, each system potentially subserving different aspects of the wakeful state. To a large extent, these interactions have not yet been fully elucidated nor are the underlying mechanisms completely understood. A number of regulatory peptides such as substance P, thyrotropin releasing hormone (TRH), corticotropin releasing hormone (CRH), vasoactive intestinal polypeptide (VIP), and neurotensin further serve to enhance and prolong excitatory activity as coagonists in the excitatory neurotransmitter pathways. This widespread diversity of pharmacological systems involved in sleep-wake regulation explains why so many different treatments affect sleep and/or wakefulness.



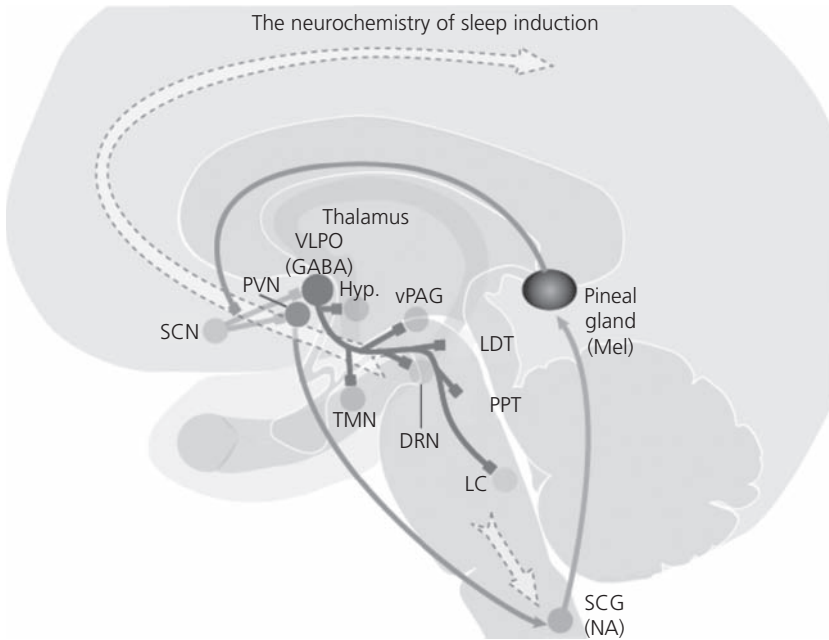
**Figure 22.1** Neurochemistry of wakefulness. During wakefulness, brainstem ascending arousal systems activate the brain by stimulation of thalamocortical transmission and of attentional processes in frontal regions, which also leads to behavioral expressions (open white arrows). The activities of different stimulating neurotransmitter systems originating in specific brainstem nuclei (including norepinephric, dopaminergic, histaminergic, and cholinergic neurons) are modulated by peptidergic systems like orexin. In this way, wakefulness can be modified by physiological conditions and circadian rhythms. BF, basal forebrain; DRN, dorsal raphe nuclei; Hypoth., hypothalamus; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; PPT, pedunculopontine tegmental nuclei; SCN, suprachiasmatic nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic area; vPAG, ventral periaqueductal gray; 5HT, serotonin; ACh, acetylcholine; DA, dopamine; GABA,  $\gamma$ -aminobutyric acid; GLU; glutamate; His, histamine; Mel, melatonin; NA, norepinephrine; Orx, orexin. This illustration is made in the framework of the pharmacology education in the Leiden University Medical Center by Dr. Kari L. Franson of the Teaching Resource Centre.

## Acetylcholine

### Wakefulness

Acetylcholine plays a unique role in the sleep-wake cycle, since this neurotransmitter not only promotes wakefulness but also facilitates REM sleep. Cholinergic neurons in the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei have a major rostral pathway that projects densely onto medial and intralaminar thalamic nuclei which, in turn, facilitate cortical activation. In particular, acetylcholine (ACh) activates nicotinic and muscarinic  $M_1$  receptors on glutamatergic thalamocortical relay neurons to facilitate cortical activation and fast cortical rhythms. This effect is further enhanced by  $M_2$  receptor-mediated inhibition of

GABA-containing thalamic reticularis neurons. A minor ventral projection pathway leads to the basal forebrain, posterior hypothalamus, and brainstem reticular formation. From the basal forebrain there is also a dense cholinergic projection to the cortex, amygdala, and hippocampus. The cholinergic tegmental and basal forebrain neurons are active during waking, while their firing is reduced with increasing depth of sleep.

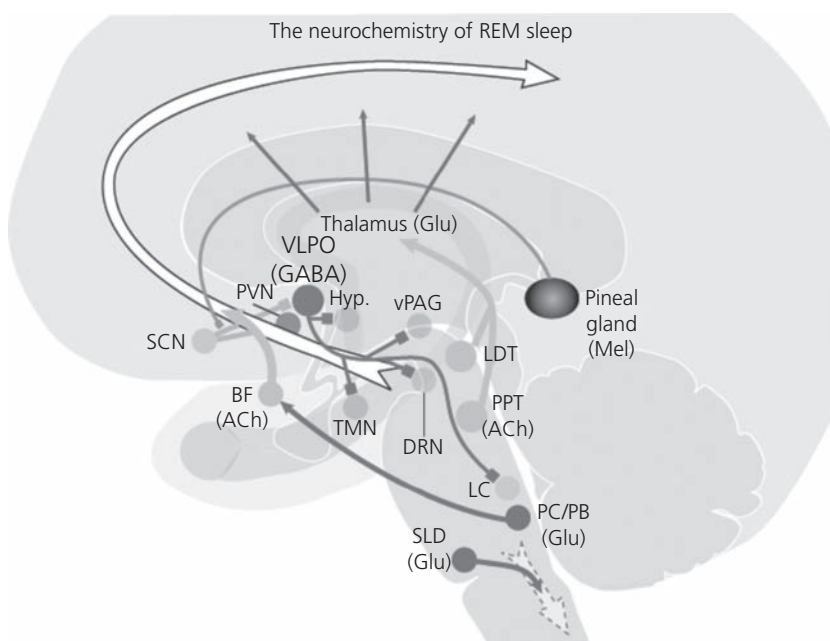


**Figure 22.2** Neurochemistry of sleep induction. The light-dark cycle has an influence on sleep and wakefulness through the suprachiasmatic nucleus (SCN). This “biological clock” controls the rhythmicity of melatonin release in the pineal gland through polysynaptic pathways. During light, the SCN suppresses the hypothalamic paraventricular nucleus (PVN) through GABA-ergic projections. When night falls, the SCN becomes less active (hence pale shade) and the PVN is disinhibited. This leads to melatonin production in the pineal gland, mediated by sympathetic (norepinephric) nerve projections that originate in the superior cervical ganglion. Elevated melatonin levels (together with darkness and several neurochemical factors that are not shown in the figure) cause a disinhibition of the ventrolateral preoptic area of the anterior hypothalamus (VLPO). This area is relatively inactive during wakefulness, but during sleep induction it exerts an inhibitory mainly GABA-ergic drive (bright VPLO with strongly shaded connecting arrows) on all major arousing neurotransmitter systems (indicated by transparent (less active) brainstem nuclei). DRN, dorsal raphe nuclei; Hyp., hypothalamus; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; PPT, pedunculopontine tegmental nuclei; PVN, paraventricular nucleus; SCG, superior cervical ganglion; SCN, suprachiasmatic nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic area; vPAG, ventral periaqueductal gray; GABA,  $\gamma$ -aminobutyric acid; Mel, melatonin, NA, norepinephrine. This illustration is made in the framework of the pharmacology education in the Leiden University Medical Center by Dr. Kari L. Franson of the Teaching Resource Centre.

Acetylcholine or cholinergic agonists, both nicotinic and muscarinic, produce prolonged wakefulness when administered during the wake period, which is associated with cortical activation and desynchronized EEG activity. Muscarinic antagonists, however, enhance low frequency synchronized activity in the EEG. The cholinergic cell loss in the basal forebrain in Alzheimer's disease is also associated with EEG slowing.

### REM sleep

The firing frequency of cholinergic LDT/PPT neurons is also increased during REM sleep. In this state, there is striking cortical activation in the absence of behavioral arousal. Cholinergic agonists such as carbachol injected into the pontomesencephalic tegmentum also produce cortical



**Figure 22.3** Neurochemistry of REM sleep. Acetylcholine is not only involved in waking, but is also important in REM sleep. Cholinergic neurons (pale arrows) facilitate thalamocortical activation, which produces some of the characteristic cortical rhythms observed in the sleep EEG. This cortical stimulation does not lead to behavioral manifestations, because the brainstem systems that mediate motor activity are inhibited during physiological REM sleep (dark arrows and transparent nuclei). Muscle tone is further reduced by glutamatergic projections from the sublateralodorsal nucleus in the pons. BF, basal forebrain; DRN, dorsal raphe nuclei; Hypoth., hypothalamus; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; PC/PB, pericoeruleus and parabrachial nuclei; PPT, pedunculopontine tegmental nuclei; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SLD, sublateralodorsal nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic area; vPAG, ventral periaqueductal gray; ACh, acetylcholine; GABA,  $\gamma$ -aminobutyric acid; GLU, glutamate; Mel, melatonin. This illustration is made in the framework of the pharmacology education in the Leiden University Medical Center by Dr. Kari L. Franson of the Teaching Resource Centre.

activation with muscle atonia, akin to a REM-like state. In the brainstem reticular formation, acetylcholine excites glycinergic medullary neurons involved in motor inhibition while inhibiting those reticulospinal neurons that excite motor neurons to produce the striking atonia of REM sleep. The REM-enabling cholinergic neurons are inhibited by norepinephrine and to a lesser extent serotonin and histamine, explaining the REM-suppressant effects of norepinephric and serotonergic antidepressants. During waking there is a balance between ACh-mediated and norepinephrine-mediated neurotransmission, safeguarding a waking state with stimulation of both muscle tone and cortical activation.

### **Cholinergic drug effects**

Many older drugs affect the cholinergic system, usually as a secondary feature due to lack of pharmacological specificity. Such poorly specific drugs include many tricyclic antidepressants which often also inhibit H<sub>1</sub>-receptors, making it difficult to attribute their sedative properties to either one of these effects. Primary muscarinic antagonists are sometimes used as anti-emetics or to reduce urinary stress incontinence and may cause sedation if they penetrate the blood–brain barrier. This explains why scopolamine used for motion sickness causes much more sleepiness than other potent antimuscarinic drugs like atropine, used as an anti-arrhythmic, or most antimuscarinic bladder spasmolytics such as oxybutinin, darifenacin, and tolterodine. Centrally active nicotinic agonists are used to treat tobacco addiction. They often cause insomnia, related both to their stimulant activity and to the effects of nicotine withdrawal. Cholinesterase inhibitors used for peripheral indications such as intestinal and bladder atonia or neuromuscular transmission disorders usually do not penetrate the blood–brain barrier and hence generally do not impair the sleep–wake cycle. Centrally active cholinergic drugs are used as cognitive enhancers in dementia. Due to their stimulant actions, they might be expected to impair sleep although some demented patients, paradoxically, experience sedation and sleep more soundly.

### **Histamine**

Histaminergic neurons in the mammillary bodies of the posterior hypothalamus stimulate cortical activation both through diffuse rostral projections and by depolarizing or exciting multiple elements of the various arousal systems. They discharge during wakefulness, decrease firing during slow-wave non-REM sleep (SWS) and cease firing altogether during REM sleep. A decrease in histaminergic brain activity appears to be linked to reduced consciousness and not to sleep-related loss of muscle tone. Evidence for the functional role of histamine in awakening as well as in the maintenance of waking also comes from histidine decarboxylase knockout mice which are slower to wake than wild

types and have more difficulty staying awake. Centrally acting  $H_1$  antihistamines are known for their sedative and sleep-inducing properties.  $H_2$  receptors do not appear to play a role in sleep and waking, whereas inhibition of  $H_3$  receptors, located as autoreceptors on histaminergic terminals and as heteroreceptors on monoaminergic terminals, also reduce cortical activation and waking.

### **Histaminergic drug effects**

$H_1$  antagonists are widely used to treat allergies. The older compounds in this class usually had such strong sedative properties that they were also widely used to treat insomnia. Newer so-called “nonsedating” antihistaminergics do not penetrate the blood–brain barrier as readily but are still often associated with sedation and sleepiness. In children, however, paradoxical insomnia can be observed. Many older and poorly selective central nervous system active drugs including some antipsychotics and anti-emetics have prominent secondary antihistaminergic properties that contribute to their sedative side-effect profile. Particularly for some antidepressants, these sedative antihistaminergic effects override the stimulant pharmacological properties associated with other elements of their pharmacological profile. Examples include noradrenergic facilitation by NE  $\alpha_2$  blockade by mianserin, or norepinephrine reuptake inhibition by amitriptyline or clomipramine. A number of  $H_2$ -receptor blocking antacids such as famotidine cause mild insomnia in some patients. This may be related to a consequence of antacid activity itself, since most proton pump inhibitors can also cause mild sleep impairment through unclear (vagal?) mechanisms.

### **Norepinephrine**

Norepinephric cell bodies in the locus coeruleus (LC) stimulate cortical activation and behavioral arousal by diffuse projections through the cortex, hippocampus, thalamus, hypothalamus, brainstem, and spinal cord, exciting wake-promoting target neurons through  $\alpha_1$  postsynaptic receptors. Inactivation of the norepinephric locus coeruleus leads to ipsilateral muscle atonia and to hippocampal theta activity, simplistically suggesting that norepinephrine may somehow play a role in connecting the brain to the body. This could be particularly relevant during REM sleep when brain activity is intense in the absence of conscious thought or movements. In keeping with this concept, LC neurons discharge during waking, particularly during high levels of activity, decrease firing during slow-wave sleep and cease firing during REM sleep. Drugs that affect the norepinephric system have contributed valuable information on the role of this system in the sleep-wake cycle. For example, norepinephric  $\alpha_1$  antagonists facilitate sleep onset. Drugs with this mechanism of action

such as doxazosin and prazosin are sometimes used clinically as vasodilating antihypertensives. Such agents not only cause sedation but may also be useful to treat insomnia and abnormal dreams in post-traumatic stress syndrome. Peripheral  $\alpha_1$  antagonists like alfuzosine and terazosine licensed to treat urinary retention may also cause sedation, probably because they penetrate the brain to some extent. Drugs blocking the pre-synaptic  $\alpha_2$  autoreceptor (yohimbine) delay sleep through norepinephric disinhibition.

### **Epinephric drug effects**

Compounds such as clonidine that stimulate inhibitory  $\alpha_2$  autoreceptors on norepinephric neurons reduce norepinephric activity and are sometimes used for treatment-resistant hypertension. Their use, however, is limited by their strong sedative effects. Presynaptic  $\alpha_2$  inhibition also reduces melatonin production which may explain why occasionally insomnia is paradoxically reported in addition to, or rather than, sedation. Centrally acting antihypertensives such as rilmenidine and moclonidine that modulate the imidazoline receptor, related to the  $\alpha_2$  receptor, have similar effects. Drugs that either activate the release or block the reuptake of norepinephrine, including amphetamines, viloxazine, and reboxetine, enhance or prolong wakefulness and can be used to treat the hypersomnolence of narcolepsy. If used recreationally or for other indications such as depression or attention deficit disorder, these stimulant effects can lead to insomnia. Many older antidepressants also inhibit norepinephrine reuptake but often have other secondary more sedative, usually antihistaminergic, pharmacological properties that may either compensate for the activating effects of norepinephric stimulation or cause mixed effects of sedation and insomnia in a clinical population or even in the same patient.

Beta-adrenergic antagonists are widely used to treat hypertension, chronic heart failure, and certain types of cardiac arrhythmia. Beta-blockers are also used as symptomatic treatments for essential tremor and anxiety. These "tranquilizing" effects are at least partly due to reduction of the peripheral associations of stress and anxiety such as diminished tachycardia and palpitations. Many beta-blockers also penetrate the central nervous system where they may cause a reduction in the diurnal increase of melatonin in the afternoon and early evening, normally facilitating the sleep phase. Probably as a result, many beta-blockers cause sleep disturbances like abnormal and vivid dreams, particularly early during their treatment. These side effects are most frequent with lipophilic beta-blockers, although some typical hydrophilic drugs like atenolol and celiprolol can also impair certain aspects of sleep.

## Serotonin

Serotonin was originally postulated by Jouvet to be the most important neurotransmitter involved in sleep processes, based largely on the observation that depletion of serotonin in cats resulted in sleep suppression. However, serotonergic neurons, concentrated in the brainstem dorsal raphe nuclei, discharge maximally during waking, decrease their discharge during slow-wave sleep and virtually cease firing during REM sleep, suggesting that the highest extracellular 5-HT levels should be found during waking. This neurophysiological finding has subsequently been corroborated by microdialysis studies. The notion that serotonin promotes wakefulness is also confirmed by drugs that enhance serotonergic transmission by inhibiting presynaptic serotonin reuptake. Sleep is promoted by inhibition of serotonergic activity, for instance by activating presynaptic inhibitory 5-HT<sub>1a</sub> autoreceptors by direct injection of the 5-HT<sub>1a</sub> agonist 8-OH-DPAT into the dorsal raphe nuclei. On the other hand, activation of postsynaptic 5-HT<sub>1a</sub> by systemic exposure to 8-OH-DPAT enhances waking. Similarly, antagonists of 5-HT<sub>2a</sub> and 5-HT<sub>2c</sub> receptors increase slow-wave sleep.

## Serotonergic drug effects

The important and complex role of serotonin in the regulation of the sleep-wake cycle is reflected by the fact that many serotonergic drugs have an impact on sleep or wakefulness, frequently on both aspects. The serotonergic system is also involved in a wide range of other physiological functions, and drugs that target this system are encountered in many different therapeutic areas. In addition, many of these drugs show only limited selectivity for the dozen or so different subtypes of serotonin receptors. Thus, triptans used for acute migraine are highly selective 5HT<sub>1b/d</sub>-receptor agonists, but the fact that most of them can cause some sedation is probably mediated by other 5HT receptor subtypes. Methysergide is an older ergotamine used for migraine and related headaches with inhibitory effects on 5HT<sub>2b</sub> receptors that can lead to both insomnia and sedation. 5HT<sub>2</sub> antagonists such as the vasodilator ketanserin promote sleep and cause sedation. Most atypical antipsychotic drugs are 5HT<sub>2</sub> antagonists in addition to being dopamine antagonists. Although most of these drugs cause sleepiness, this property varies considerably, mainly depending on additional pharmacological characteristics such as antihistaminergic effects. Some D<sub>2</sub>/5HT<sub>2</sub> inhibitors such as tiapride or the diphenylbutylpiperidenes (pimozide) do not cause significant sedation. Selective 5HT<sub>3</sub> antagonists including ondansetron also do not affect sleep and waking, although less selective antiemetics such as granisetron or metoclopramide, which also block D<sub>2</sub> receptors, can cause sedation. After acute administration, almost all antidepressants cause a secondary



or primary increase in synaptic serotonin levels, either by reducing degradation (monoamine oxidase inhibitors), by inhibiting synaptic reuptake, or by (indirectly) stimulating serotonin release. Antidepressants are well known for their REM-reducing effects, a property that is sometimes used as a biomarker to predict the antidepressant properties of novel drugs in development. The widespread and nonselective synaptic serotonin increase caused by most antidepressants can lead to a variety of sleep-wake abnormalities, including not only acute or withdrawal insomnia but also sedation and abnormal dreams, bruxism, and yawning. As a clinical guideline, serotonin activation will generally promote wakefulness and inhibition will cause sedation, particularly if 5HT<sub>2</sub> receptors are involved. Since many of the diseases themselves that are treated with serotonergic medications can also affect sleep or alertness, pragmatic dose reductions or switching to nonserotonergic alternative treatments can provide support for the involvement of a serotonergic drug if a patient complains of sedation or insomnia.

## Dopamine

Mesencephalic dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) project to the striatum, basal forebrain, limbic areas, thalamic subnuclei, and frontal cortex. Discharge rates, particularly tonic burst activity, correlate with aroused and positively rewarding states. This happens both during waking and REM sleep, suggesting that dopaminergic activation leads to central arousal associated with reward, but not necessarily to behavioral arousal and increased postural muscle tone. Unlike the histaminergic and norepinephric neurons, there is much less variation in the firing rates of dopaminergic neurons over the 24-hour sleep-wake cycle, further indicating that dopamine plays a different role in sleep and waking compared to the other monoaminergic neurotransmitters. Dopamine reuptake blockers and dopamine releasers combine arousing and psychostimulant rewarding effects through activation of dopamine receptors in the ventral tegmental area. This probably accounts for the abuse potential of cocaine and amphetamine, for example. They can also cause profound insomnia. Although most dopamine reuptake inhibitors also inhibit the reuptake of norepinephrine, it is evident from studies with selective dopamine reuptake inhibitors and with dopamine receptor knockout mice that the wake-promoting effects of these compounds are to a large extent due to elevation of synaptic levels of dopamine. In animals, dopamine D<sub>1</sub> agonists induce behavioral arousal, whereas D<sub>2</sub> receptor agonists give rise to biphasic effects with low doses reducing wake time and augmenting slow-wave sleep and REM sleep. Large doses have opposite effects.

**Dopaminergic drug effects**

The complex sleep-wake effects of dopamine, dysregulation of dopaminergic systems in Parkinson's disease and other neuropsychiatric conditions, and the incomplete subtype selectivity of most dopaminergic drugs, all contribute to divergent and often biphasic effects of dopamine precursors and agonists on sleep and wakefulness. Dopaminergic medications can lead to sedation or sleep attacks in some patients while promoting psychomotor activity and causing insomnia in others. Antiparkinson drugs often cause abnormal dreams or nightmares. In patients with impaired sleeping patterns related to dopamine deficiency such as Parkinson's disease or restless legs syndrome, dopamine agonists can also improve sleep. In other patients, the activating effects of peak plasma levels of dopaminergic treatments can even at therapeutic levels lead to sleep impairment.

Reduction of dopamine as observed in patients with Parkinson's disease is generally associated with sleepiness. Similarly, inhibition of dopamine receptors by D<sub>1</sub> and D<sub>2</sub> receptor antagonists or reduction of dopaminergic tone by activation of D<sub>3</sub> autoreceptors induces somnolence. Central dopaminergic antagonists are mainly used to treat psychosis, although neuroleptics and atypical antipsychotics are also applied in anesthesia and for neuropathic pain and dystonia. Peripheral dopaminergic antagonists are used to treat nausea and vomiting but they can also cause central nervous system effects if they penetrate the blood-brain barrier sufficiently. This can be an issue in patients with central nervous system diseases or in susceptible individuals, particularly the elderly and children. Cotreatment with medications that disrupt the blood-brain barrier or inhibit p-glycoprotein pump function may enhance these effects. Neurokinin-1 (NK1) activation enhances the activity of dopaminergic neurons. NK<sub>1</sub> antagonists, which have been successfully developed as anti-emetics (aprepitant) and are being evaluated for psychiatric indications, can cause sedation and less frequently insomnia with abnormal dreams. The sedating effects of antipsychotic agents are not only due to inhibition of D<sub>2</sub> receptors, since most antipsychotics also have prominent inhibitory effects on other wake-related receptor types. These include 5HT<sub>2</sub> receptors for atypical antipsychotics or H<sub>1</sub> receptors for most of the older neuroleptics.

**Glutamate**

Most of the thalamocortical projection relay neurons that stimulate the cortical mantle, after activation by both acetylcholine and biogenic amines, have glutamate as their neurotransmitter in common with many of the basal forebrain neurons projecting onto the cortex. Subcortical glutamate levels in the nucleus accumbens, for example, are also high during waking and low during slow-wave sleep and REM sleep. Direct

or indirect glutamate inhibition will generally cause sedation and sleepiness, but few specific medications have an isolated or predominant effect on glutamatergic transmission because of adverse effects. This widespread excitatory neurotransmitter is physiologically extremely important and general manipulations of its levels therefore lack specificity. However, inhibition of specific glutamate NMDA receptors usually cause sedation. Magnesium acts as a physiological inhibitor of glutamate-NMDA-cation channels by blocking the central pore of this pentameric peptide channel, thus preventing intracellular passage of  $\text{Na}^+$  or  $\text{Ca}^{2+}$  and neuronal excitation. For this reason, magnesium is used intravenously to treat seizures related to pre-eclampsia in pregnancy. Magnesium preparations are also used as antacids and have the potential to cause sedation and sleepiness. Noncompetitive glutamate NMDA antagonists are used for various indications and almost all are sedative. Memantine for dementia, amantadine for Parkinson's disease and influenza A, riluzole for amyotrophic lateral sclerosis, acamprosate for alcohol addiction, ketamine and phencyclidine for anesthesia, and dextromethorphan in cough syrups can all cause drowsiness in clinical doses, albeit to variable degrees. Although some antiepileptic drugs such as levetiracetam and possibly lamotrigine inhibit glutamate release (in the former case by synaptic vesicle 2-inhibition), these compounds also seem to have other pharmacological effects on nerve conduction that are related to their sedative adverse effect profile. These other effects may explain why lamotrigine has stimulatory properties in about one-third of patients, helping to reduce the side effects of sedative comedication but also potentially causing sleep disturbance.

### **Sleep regulators**

Orexin (hypocretin)-producing neurons in the lateral hypothalamus heavily innervate the brainstem arousal nuclei and appear to play an important role in the stabilization of the wakeful state. They are inhibited by the sleep-promoting centers of the lateral preoptic area. Currently, there are no drugs on the market which act primarily through the orexin system but an active area of research is focussed on finding orexin antagonists for the treatment of insomnia, the most advanced compound to date being almorexant.

Melatonin is a pivotal regulator of circadian rhythms, including the sleep-wake cycle. Its production and release mainly occur during the early part of the dark cycle. Retinal fibers projecting to the suprachiasmatic nucleus of the hypothalamus play an important role in adjusting the clock mechanism. During the evening and early night, this "physiological clock" stimulates the superior cervical ganglion which, in turn, activates melatonin production in the pineal gland through norepinephric sympathetic nerve fibers. Melatonin-1a receptors in the hypothalamus convey the

information about the light-dark cycle to other centers driving circadian physiological functions. Although melatonin itself penetrates the blood-brain barrier only poorly and variably, it is widely used as a sleep-enabling “food supplement.” Several melatonin agonists have been developed or are in various stages of assessment for insomnia. These include ramelteon, agomelatin which is also a 5HT<sub>2c</sub> antagonist, and tasimelteon. Melatonin production is reduced by a number of different drugs including beta-blockers, corticosteroids, NSAIDs, cannabinoids, and benzodiazepines, which at least partly explains why these drugs can disrupt normal sleeping patterns. Other medications can cause a phase shift in melatonin release such as the phase advance produced by long-term levodopa treatment. Melatonin is metabolized through the cytochrome P450 system (mainly CYP1A2) and drugs that inhibit these liver enzymes can also prolong the activity of melatonin, particularly when production is at its peak early in the evening. These pharmacokinetic interactions can modulate the sleep effects of drugs that inhibit CYP1A2 such as caffeine, fluvoxamine, and artemisinin. CYP1A2 inducers generally do not have a functionally significant impact on endogenous melatonin release, although many such inducers including barbiturates and smoking have prominent sleep effects of their own.

### **The opioid system**

Opioids act at a variety of receptors, the main subtypes being mu, kappa, and delta. All three of these receptor subtypes appear to be involved in the analgesic effect of opioids, whereas the mu subtype plays a larger role, compared with the kappa subtype, in respiratory depression. Respiratory depression is one of the more serious adverse effects of opioids, particularly during sleep. Opioids act directly on the brainstem respiratory centers through mu and delta receptors and at chemoreceptors through mu receptors. Opioids depress the pontine and medullary centers involved in the regulation of respiratory rhythmicity. Individuals with pulmonary disease or obstructive sleep apnea are known to be at greater risk for sustained hypoxemia during sleep. Concomitant use of other sedatives, in particular hypnotics, increases the risk for potentially fatal respiratory depression. Although there is widespread belief that tolerance to the sedating effects of opioids develops with chronic use, there are no objective data to support this claim. The limited polysomnograph data available indicate that opioids decrease REM sleep and slow-wave sleep. Subjective quality of sleep, however, is often improved in patients under opioid analgesics, but this is probably a secondary effect of improved pain control. The degree of sedation may depend on the specific drug, dosage, and duration of use, as well as on the severity of the underlying condition. In addition, the elderly appear particularly sensitive to opioids. Opioid

mu antagonists used to treat overdosing and opioid or alcohol addiction can cause insomnia and other signs of acute drug abstinence.

### **Drugs affecting neuronal conduction and signal-effect coupling**

Neuronal conduction and electrochemical signaling are essential for all central nervous system activities at all stages of the sleep-wake-cycle. It is not surprising therefore that drugs that affect neuronal conduction or the translation of the signal into a biological effect can also have an impact on wakefulness and sleep. Essentially, therefore, every agent that affects one of the numerous cell membrane conductances can change sleep-wake regulation, depending on how much it penetrates the brain. One of the most important conductances in this regard is mediated by the voltage-gated calcium (CaV) channels that subserve a large spectrum of physiological functions. N- and P/Q-type channels are the main subtypes of the calcium channel concentrated at nerve terminals, where they support the release of synaptic vesicles in synaptic transmission. L-type channels come in different varieties (CaV1.1 to CaV1.4) and are involved in different physiological processes, ranging from excitation-contraction coupling to synaptic plasticity and retinal processing. R-type channels may be involved in neurotransmitter release and repetitive firing. T-type channels play a role in cardiac pacing, thalamocortical oscillations, hormone secretion, and smooth muscle contraction. They also contribute to regulation of intracellular calcium levels. The involvement of T-type channels in thalamocortical oscillations suggests an interesting link to sleep rhythms and spike-wave discharges, especially since thalamocortical circuits play an important role in both sleep and epilepsy. These channels are inhibited by the antiepileptics ethosuximide and valproate, drugs usually highly effective in absence epilepsy and often causing sedation. The effects of these drugs on sleep are less clear, however, with stabilization of sleep phases in some studies and fragmentation in others.

The involvement of voltage-gated calcium channels in many different biological processes makes them interesting targets for physiological research and pharmacotherapy. L-type CaV-channels, in particular, are unique substrates for a wide variety of treatments. The lack of tissue selectivity and functional homogeneity might be expected to produce significant undesired side effects that can be quite variable in character and intensity. L-type voltage-dependent calcium channel inhibitors such as verapamil and dihydropyridines like nifedipine and nitrendipine are widely used to treat hypertension and cardiac insufficiency. These drugs regularly lead to insomnia and nervousness. The antihypertensive amlodipine, the bladder spasmolytic flavoxate, and both pregabalin and gabapentin, used for epilepsy and neuropathic pain, affect different types

of L-type voltage-dependent calcium channels and are all known to be associated with sedation. The drug flunarizine used for vertigo is a non-selective voltage-gated channel inhibitor potentially causing sleep impairment, although these effects are usually overshadowed by the sedative effects of its concomitant antihistaminergic properties. Similar effects are shown by the spasmolytic dantrolene, which blocks calcium release from cytoplasmic stores by inhibition of ryanodine.

### **Antiepileptics**

In general, antiepileptic drugs are developed to reduce neuronal conduction and signal transmission, preventing or interrupting the propagation of epileptic seizures. However, the underlying pharmacological mechanisms of action are often incompletely understood. A number of the most potent antiepileptics block voltage-dependent sodium channels. Examples include carbamazepine, topiramate, zonisamide, and the SV2 inhibitors. Valproate and phenytoin also inhibit voltage-gated calcium channels. The impact of antiepileptics on nerve conduction can lead to variable degrees of dose-dependent sedation. Many antiepileptic drugs have prominent effects on sleep, although the evaluation of these effects in clinical populations of epileptic patients is complicated by arousals due to nocturnal interictal or seizure activity.

## **Neuropharmacology of non-REM sleep**

While the activation of multiple neurotransmitter systems has been implicated in various aspects of waking, sleep pharmacology has been dominated by a single neurotransmitter, namely,  $\gamma$ -aminobutyric acid (GABA). Despite an intensive search for other sleep-promoting substances, there has been limited success in the discovery of these so-called “hypnogens.” It is evident, however, that sleep is regulated not only by circadian factors but also by homeostatic control mechanisms. With increasing time awake, a sleep debt and increased drive to sleep builds up. It is likely that humoral factors are involved in this homeostatic control. Recent evidence suggests that purinergic receptors with adenosine responsivity may play an important role in this mechanism.

### **Gamma amino butyric acid**

Gamma amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. Contrary to bioamine neurotransmitters, which are produced in a small number of highly specialized midbrain and brainstem nuclei, GABA-ergic neurons are widespread throughout the brain. About 40% of central neurons contain GABA and

30% of synapses bind GABA. A small group of GABA-ergic cells in the ventrolateral preoptic area (VLPO) as well as in the adjacent basal forebrain (BF) and preoptic area (PO) appear to be crucial for the control and maintenance of non-REM sleep. Certainly, lesions in this region result in severe insomnia. Furthermore, neurons in these areas fire at higher rates during sleep than during waking and show high c-fos expression during sleep recovery after sleep deprivation. Basal forebrain sleep-promoting neurons project rostrally to the cortex alongside wake-promoting ACh-containing neurons. Their firing activity correlates positively with delta EEG activity and negatively with gamma EEG activity. VLPO GABA-ergic neurons also project caudally into the posterior lateral hypothalamus where they synapse onto orexinergic neurons. Further down they inhibit histamine-containing neurons in the tuberomammillary nucleus and brainstem norepinephric and serotonergic neurons in the locus coeruleus and dorsal raphe nuclei. Sleep-active VLPO neurons, in turn, are under inhibitory control from norepinephrine, histamine, and acetylcholine systems. Accordingly, these neurons are inhibited during waking and are disinhibited when monoaminergic and cholinergic neurons decrease their discharge following the transition to drowsiness.

Local GABA-ergic neurons in the brainstem reticular formation and locus coeruleus also show increased activity during sleep. GABA-containing neurons in the caudal medullary reticular formation, projecting to the spinal cord, are active during REM sleep together with glycine-containing neurons which directly inhibit spinal motor neurons. Frontally, GABA-ergic neurons in the thalamic reticularis nucleus inhibit thalamocortical relay neurons to dampen cortical activation. Their burst pattern of discharge during sleep triggers spindle activity (12–14 Hz) and induces delta oscillations through the hyperpolarizing actions of GABA on the thalamic relay neurons.

### **Benzodiazepines**

Since their discovery around 1960, benzodiazepines have become the most important drugs for generalized anxiety disorder, insomnia, and alcohol withdrawal. They also have a prominent place in the induction and maintenance of anesthesia as well as the treatment of seizures. The clinical use of benzodiazepines in the treatment of insomnia and other nocturnal sleep disorders is discussed in chapter 5. There are three main different GABA receptors. GABA<sub>A</sub> is a ligand-gated ion channel for chloride (Cl<sup>-</sup>), GABA<sub>B</sub> is a G-protein coupled receptor, and GABA<sub>C</sub>, similar to GABA<sub>A</sub>, is found predominantly in the retina. Benzodiazepines bind to GABA<sub>A</sub> receptors and increase the affinity of GABA for the GABA-binding site. GABA<sub>A</sub> receptors are heteropentameric, consisting of five subunits surrounding the central Cl<sup>-</sup> channel. Thus far, 19 different

subunits (six  $\alpha$ , three  $\beta$ ,  $\delta$ , three  $\gamma$ ,  $\epsilon$ ,  $\pi$ , three  $\pi$ ,  $\tau$ ) have been isolated which can occur in a limited number of combinations. Benzodiazepines bind at the interface of  $\alpha$  and  $\gamma$  subunits while GABA binds to the interface of the  $\alpha$  and  $\beta$  subunit. Depending primarily on the nature of the  $\alpha$  subunit, GABA<sub>A</sub> receptors subserve different functional roles. Receptors with  $\alpha_1$  subunits are involved in sedation, amnesia, and ataxia whereas those with  $\alpha_2$  subunits in anxiolysis and myorelaxation. Alpha<sub>3</sub> and  $\alpha_5$  are relevant for muscle relaxation and ataxia while seizure suppression is observed with all  $\alpha$  subunits. The benzodiazepines show little difference in subunit selectivity, with the exception of  $\alpha_4$  and  $\alpha_5$  subunits which are insensitive to benzodiazepines. Their main therapeutic characteristics are due to differences in pharmacokinetic properties and dosage regimens. Long-acting low-level benzodiazepine dosing is used for generalized anxiety or seizure prevention, mainly in children, whereas fast-onset high-level concentrations are needed to treat status epilepticus or to induce anesthesia. Non-benzodiazepine sleep-inducing agents like zolpidem, zopiclone, and zaleplon are characterized by a rapid absorption and a high affinity for  $\alpha_1$  subunits, which are primarily associated with sedation.

Benzodiazepines do not restore normal sleep. In contrast, they suppress deep sleep and REM-sleep stages while augmenting light stage 2 sleep. This reduced sleep quality along with persisting drug plasma levels of the longer-acting compounds may cause the “hangover” effects that are frequently reported after use of benzodiazepines for insomnia. After a few weeks of daily treatment, most benzodiazepines also produce tolerance, associated with reduced efficacy and withdrawal symptoms after stopping. These withdrawal symptoms include insomnia and restlessness, which rapidly disappear after re-administration of the drug. This is an important cause for the dependency that many subjects experience after using benzodiazepines for more than 3 or 4 weeks. Very short-acting (non)benzodiazepine drugs may show less propensity for drug dependency with once-daily dosing. In general, however, most authorities recommend that prescriptions for GABA-ergic drugs for anxiety-related sleep disorders should be limited to a few weeks of uninterrupted use.

### Barbiturates

Barbiturates allosterically enhance the binding of GABA to its receptor, thereby potentially increasing and prolonging the effects of this neurotransmitter. Barbiturates also have other pharmacological effects such as reduced glutamatergic transmission that contribute to their strong central nervous system suppressant properties. Barbiturates are used in anesthesia and for the treatment or prevention of seizures, mainly as secondary treatment option. Their potency and long terminal half-life often cause prominent sedative adverse effects. Although patients seem to develop



some tolerance to these side effects during prolonged treatment, much of this is due to behavioral adaptation to the long-lasting central nervous system depression caused by this class of drug.

Several GABA-ergic drugs with other pharmacological mechanisms have been developed. These include GABA-transferase inhibitors such as vigabatrin, a rarely used antiepileptic drug; GABA-release stimulators, one mechanism of action of the GABA<sub>B</sub> agonist baclofen used for dystonia and muscle spasticity; and GABA-reuptake inhibitors such as the antiepileptic tiagabine. In general, these drugs amplify the activity of endogenous GABA and hence cause fewer adverse effects. Nonetheless, all these GABA-ergic drugs cause dose-related sedation with less marked disturbance of sleep patterns. Ethanol is an allosteric enhancer of transmembrane receptors and many of its effects are mediated by enhancement of GABA-ergic signaling. In line with this effect, ethanol primarily causes sedation but also disturbs sleep maintenance.

GABA-A antagonists could theoretically play a role in the symptomatic treatment of a range of cognitive and movement disorders but, so far, their development has been limited by proconvulsive side effects and agitation with insomnia. Flumazenil is an inverse benzodiazepine receptor agonist that is used clinically to counteract benzodiazepine overdosing. Flumazenil can impair sleep at high doses but this may also reflect acute benzodiazepine withdrawal.

### **Adenosine**

Adenosine is a degradation product of ATP, produced during cellular metabolic activity, which provides feedback on the cell's energy levels. Adenosine analogs are one of the few postsynaptic receptor agonists known to increase slow-wave sleep. This may partly be mediated by adenosine A<sub>1</sub>-induced decrease of neuronal firing and neurotransmitter release of both cholinergic basal forebrain cells and monoaminergic brainstem neurons. However, A<sub>2</sub>-receptor mediated stimulation of VLPO sleep-promoting neurons may also be involved. In the cortex and thalamus, adenosine has a hyperpolarizing effect, switching these cells into a burst firing mode associated with slow-wave sleep. Adenosine levels in the brain are higher during waking than during sleep and increase progressively with prolonged wakefulness, suggesting that adenosine might be a homeostatic sleep factor which builds up after prolonged wakefulness. Adenosine is used as a class V antiarrhythmic drug but does not penetrate the brain sufficiently to cause central nervous system effects. Phosphodiesterase (PDE) inhibitors decrease the inactivation of cyclic adenosine and guanosine monophosphates (cAMP and cGMP) and thereby prolong the active state of the cell. Caffeine, theophylline, and other methylxanthines are both nonselective PDE inhibitors and adenosine

A<sub>1</sub> receptor antagonists and thereby have a wake-promoting effect. PDE3 inhibitors like enoximone and milrinone are used to treat cardiac failure by mimicking sympathetic stimulation. PDE4 inhibitors such as ibudilast and pentoxifylline cause bronchodilation by a similar mechanism. PDE5 inhibitors including sildenafil and vardenafil are used to treat erectile dysfunction and pulmonary hypertension. Anagrelide reduces thrombocyte levels by PDE inhibition in platelets. The tissue selectivity of PDE subtypes is limited, and most of these drugs stimulate wakefulness and cause insomnia. These stimulating properties have led to the exploration of subtype-selective PDE inhibitors and adenosine antagonists as cognitive enhancers and CNS stimulants potentially for treating dementia, depression, and the negative symptoms of schizophrenia. So far, this approach seems to have been thwarted by the lack of brain selectivity for subtype selective PDE inhibitors and associated risks of insomnia, agitation, and seizures.

### **Sleep factors and immune system modulators**

Sleep factors are homeostatic substances which, as proposed for adenosine, progressively build up with the amount of waking or physical activity. Most of these compounds have originally been isolated from brains of sleep-deprived animals. Apart from nitric oxide, uridine, oleamide, and prostaglandin-D<sub>2</sub>, most sleep factors proved to be of peptidergic origin. These putative sleep factors include muramyl dipeptide, delta sleep-inducing peptide, cortistatin, somatostatin, cholecystokinin, bombesin, insulin, neuropeptide S, prolactin, gallanin, ghrelin, neuropeptide Y, growth hormone (GH), growth hormone releasing hormone (GHRH), melanin-concentrating hormone (MCH), tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), and interleukins (IL-1 $\beta$ ). In most cases the physiological mechanisms that link these modulators to the sleep-wake cycle are still poorly characterized.

Sleep-wake regulation and feeding behavior are closely linked, partly through the activation of the autonomic nervous system. Drugs that affect metabolic homeostasis also often have a significant impact on sleep or wakefulness. For instance, compounds that mimic aspects of starvation may cause insomnia. This may include lipid-lowering drugs such as statins, anorectics, and oral hypoglycemics. Since stress also causes insomnia, most drugs that can be considered as stress hormones such as corticosteroids have similar properties. The sleep effects differ considerably among the various glucocorticoids, depending on their dose levels, central nervous system penetration, and patient susceptibility. The effects of other hormones are also in line with their physiological effects. Thyroid hormones cause dose-dependent nervousness and insomnia as early signs of overstimulation. Luteinizing hormone may induce prominent sleepiness and androgens insomnia. Estrogen- or gonadotropin antagonists can also produce insomnia in some

patients, reminiscent of menopausal sleeping problems. Progestagens and estrogens, however, usually do not have significant sleep-wake side effects.

Inflammatory processes have complex effects on sleep. In general, infections promote sleep as a consequence of stimulating the immunological defense systems. At the same time, serious infections cause considerable stress activation, tending to impair normal sleep. Infections change the interactions between the immune system and brain neurochemical systems involved in sleep-wake maintenance, particularly cytokine and serotonergic pathways. Considering the complicated role of the serotonergic system on sleep, it is perhaps understandable that many anti-inflammatory, immune-modulatory and antimicrobial drugs can variously cause insomnia, sedation, or combinations of these side effects.

Almost all antiviral medications can cause insomnia and abnormal dreaming occurs in a minority of patients. At the same time, several studies have shown that these drug-related side effects are aggravated by the burden of personal psychological stress factors. Most chinolone and some macrolide antibiotics have similar side effects. The majority of antimalarial drugs can also lead to moderate sedation. Cytostatics share many aspects of their mechanisms of action with antimicrobial drugs and about one-third cause sedation, insomnia, or both at therapeutic doses, without a clear relationship to the underlying mechanism of action. About half of all cytostatic immunomodulators such as tyrosine kinase inhibitors, used to treat leukemia, and all of the angiogenesis inhibitors can cause mild insomnia although, equally, a proportion of patients can become sedated. These effects may be partly due to an interaction with the underlying disease state or to associated factors, considering the large impact of cancer or severe infections on the sleep-wake cycle. Many cytostatic antihormones, particularly aromatase inhibitors used to treat breast cancer, reduce alertness or impair sleep. Reduction of normal hormone levels could also explain why the corticosteroid antagonist mitotane causes sedation in many patients with adrenal gland carcinoma, considering the well-known opposite effects of corticosteroids.

Some prostaglandin agonists, used for induction of childbirth or abortion, and most antagonists, namely NSAIDs and salicylates, can cause either limited sedation or insomnia and sometimes abnormal dreams, provided they act long enough and penetrate the central nervous system sufficiently. The same holds true for TNF- $\alpha$  inhibitors such as infliximab or adalimumab, although other disease-modifying antirheumatic agents only seem to cause central nervous system effects at toxic drug levels. Most interferon preparations can produce mild insomnia, whether they are used to treat chronic viral infections (alpha, gamma) or multiple sclerosis (beta). For other immunological drug classes, the reports on either

sedative or sleep-impairing effects are less frequent or severe but hardly any class is completely devoid of such potential problems. The effects of most immunosuppressants or immunomodulators, therefore, can occasionally be added to the differential diagnosis of an impaired sleep-wake cycle in a susceptible patient. The highly complicated inflammation cascades are affected not only by anti-inflammatory drugs but also secondarily by other drug classes. Angiotensin converting enzyme (ACE) inhibitors, for instance, which secondarily increase bradykinin activity, can cause mild insomnia, sometimes related to cough.

### Key points

- The circadian and functional changes during the sleep-wake cycle require coordinated changes of almost all pharmacological systems in the nervous system. Consequently, most drugs acting on the central nervous system can have an impact on sleep-wake regulation.
- Sedation and insomnia are determined by how the drug's primary or secondary pharmacological characteristics interact with sleep-wake regulation. The effects are modified by drug levels in the central nervous system, and by the sensitivity of the brain for the medication.
- Centrally active anticholinergic drugs often cause sedation and memory disturbance. This is a relevant secondary pharmacological characteristic of many older compounds.
- Antihistaminergic (H1) drugs cause sleepiness in proportion to their brain penetration.
- Norepinephric agonists ( $\alpha_1$  agonists, release stimulators, reuptake inhibitors) often cause insomnia. Norepinephric  $\alpha_1$  antagonists and presynaptic (auto-inhibitory)  $\alpha_2$  agonists usually cause sedation and promote sleep.
- Serotonergic drugs are used for different indications, and many show incomplete subtype selectivity. Such drugs can cause insomnia, sedation, or both.
- Dopamine  $D_1$  agonists induce behavioral arousal, whereas  $D_2$  receptor agonists give rise to biphasic effects with low doses reducing wake time and augmenting slow-wave sleep and REM sleep. Large doses have opposite effects.  $D_2$ -antagonists induce some sedation, which for many antipsychotic drugs is also due to secondary antihistaminergic or -serotonergic effects.
- GABA is the primary inhibitory neurotransmitter in the central nervous system, and a small group of ventrolateral and basal GABA-ergic cells are involved in the control and maintenance of non-REM sleep. Benzodiazepines and barbiturates are GABA-ergic coactivators.
- Sleep factors like adenosine build up with the amount of waking and physical activity. Phosphodiesterase inhibitors and adenosine A1 receptor antagonists like caffeine and theophylline are activating and wake-promoting drugs.
- Sleep-regulating hormones convey information about the light-dark cycle (melatonin) and coordinate the different neurophysiological systems involved in circadian rhythms (orexin). Some drugs affect wakefulness or sleep by interfering with these mechanisms. Beta-blockers reduce melatonin release and often cause abnormal dreams.

- The restorative function of sleep involves an intensive cross-talk with other fundamental homeostatic processes, such as immunological, metabolic, endocrine, and autonomic nervous systems. This complexity is reflected by the high frequency of sedation, sleepiness, insomnia, and abnormal dreaming during treatment with medications for infections, malignancies, and auto-immune, cardiovascular, and other systemic conditions.

## Suggested further reading

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- 4 Espana SA, Scammell TE. Sleep neurobiology for the clinician. Sleep 2005; 27:811–820.
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## APPENDIX A

# Sleep diagnoses

Sleep diagnoses according to the 2<sup>nd</sup> edition of the *International Classification of Sleep Disorders*. To enable the coding of sleep disorders in the ICD-10, a 'cross-walk' is provided towards the ICD-10 codes.

ICSD-2	ICD-10	ICD-10 Code
<b><i>Insomnia</i></b>		
Adjustment insomnia	Non organic insomnia	F51.0
Psychophysiological insomnia	Non organic insomnia	F51.0
Paradoxical insomnia	Non organic insomnia	F51.0
Idiopathic insomnia	Idiopathic insomnia	G47.0
Inadequate sleep hygiene	Non organic insomnia	F51.0
Behavioral insomnia of childhood	Non organic insomnia	F51.0
Insomnia due to drug or substance	Insomnia (organic)	G47.0
Insomnia due to alcohol	Insomnia (organic)	G47.0
Insomnia due to medical condition	Insomnia (organic)	G47.0
Insomnia due to mental disorder	Non organic insomnia	F51.0/F51.8
Insomnia not due to substance or known physiological condition	Organic insomnia	G47.0
Physiological (organic) insomnia, unspecified	Organic insomnia	G47.0
<b><i>Sleep related breathing disorders (SRBD)</i></b>		
<b>Central Sleep apnea syndromes (CSAS)</b>		
Primary central sleep apnea	Central sleep apnea syndrome	G47.30
Central sleep apnea due to Cheyne Stokes breathing pattern	Periodic breathing (Cheyne Stokes breathing)	R06.3
Central sleep apnea due to high-altitude periodic breathing	Central sleep apnea syndrome	G47.30/ R06.3
Central sleep apnea due to medical condition not Cheyne Stokes	Central sleep apnea syndrome	G47.30
Central sleep apnea due to drug or substance	Central sleep apnea syndrome	G47.30
Primary sleep apnea of infancy	Sleep apnea in new borns	P28.3

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ICSD-2	ICD-10	ICD-10 Code
<b>Obstructive sleep apnea syndrome (OSAS)</b>		
Obstructive sleep apnea, adult	Obstructive sleep apnea syndrome	G47.31
Obstructive sleep apnea, pediatric	Obstructive sleep apnea syndrome	G47.31
<b>Sleep related hypoventilation/hypoxemia syndrome</b>		
Sleep related nonobstructive hypoventilation, idiopathic	Sleep related hypoventilation syndrome	G47.32
Congenital central alveolar hypoventilation syndrome	Congenital central alveolar hypoventilation syndrome	G47.32
<b>Sleep related hypoventilation/hypoxemia due to:</b>		
Lower airways obstruction	Sleep related hypoventilation syndrome	G47.32/J44.9
Neuromuscular and chest wall disorders	Sleep related hypoventilation syndrome	G47.32
Pulmonary parenchymal or vascular pathology	Sleep related hypoventilation syndrome	G47.32
<i>Other sleep related breathing disorders</i>	Sleep apnea, unspecified	G47.38
<b><i>Hypersomnias of central origin not due to a circadian rhythm disorder, sleep related breathing disorder, or other cause of disturbed nocturnal sleep</i></b>		
Narcolepsy with cataplexy	Narcolepsy with cataplexy	G47.4
Narcolepsy without cataplexy	Narcolepsy with cataplexy	G47.4
Narcolepsy due to medical condition with cataplexy	Narcolepsy with cataplexy	G47.4
Narcolepsy unspecified	Narcolepsy with cataplexy	G47.4
Idiopathic hypersomnia with long sleep time	Hypersomnia (idiopathic)	G47.1/F51.1
Idiopathic hypersomnia without long sleep time	Hypersomnia (idiopathic)	G47.1/F51.1
Behaviorally induced insufficient sleep syndrome	Sleep disorders, not otherwise classified	F51.8
Hypersomnia due to medical condition	Sleep disorders, not otherwise classified	G47.9
Hypersomnia due to drug or substance	Hypersomnia (idiopathic)	G47.1

(Continued)

ICSD-2	ICD-10	ICD-10 Code
Hypersomnia due to alcohol	Hypersomnia (idiopathic)	G47.1
Hypersomnia not due to substance or known physiological condition	Non organic hypersomnia	F51.9
Physiological (organic) hypersomnia, unspecified	Sleep disorders not otherwise classified	G47.9
Recurrent hypersomnia: Kleine-Levin syndrome	Kleine-Levin syndrome	G47.8
Recurrent hypersomnia: menstrual related hypersomnia	Sleep disorders not otherwise classified	G47.9
<b><i>Circadian rhythm sleep disorders:</i></b>		
Circadian rhythm sleep disorder	Circadian sleep rhythm disorders	G47.2
delayed sleep phase type	Circadian sleep rhythm disorders	G47.2
advanced sleep phase type	Circadian sleep rhythm disorders	G47.2
irregular sleep wake type	Circadian sleep rhythm disorders	G47.2
nonentrained type (free running)	Non organic disturbed sleep	F51.2 p
jet lag type	wake rhythm	
Circadian rhythm sleep disorder due to medical condition or drug or substance	Sleep disorder, not otherwise specified	G47.2
<b><i>Parasomnias</i></b>		
<b>Disorder of arousal (NREM associated)</b>		
Confusional arousals	Sleep disorder, not otherwise specified	G47.8/F51.8
Sleepwalking	Sleepwalking	F51.3
Sleep terrors	Sleep terrors	F51.4
<b>REM associated</b>		
REM sleep behavior disorder	Sleep disorders not otherwise classified	G47.8
Recurrent isolated sleep paralysis	Sleep disorders not otherwise classified	G47.8
Nightmare disorder	Nightmares	F51.5
<b>Other parasomnias</b>		
Sleep related dissociative disorder	Sleep disorders not otherwise specified	F44.x
Sleep enuresis	Enuresis psychogenic (only in children)	F98.0/R33.8
	Sleep disorders not otherwise specified	F51.8
Sleep related groaning (catathrenia)	Sleep disorders not otherwise specified	G47.8/F51.8
Exploding head syndrome	Sleep disorders not otherwise specified	G47.8
Sleep related hallucinations	Sleep disorders not otherwise specified	G47.8



ICSD-2	ICD-10	ICD-10 Code
Sleep related eating disorder	Sleep disorders not otherwise specified	G47.8/F51.8
Not otherwise classified (unspecific) parasomnia	Sleep disorders not otherwise specified	G47.8
Parasomnias due to drug or substance	Sleep disorders not otherwise specified	G47.8
Parasomnias due to medical condition	Sleep disorders not otherwise specified	G47.8
<b><i>Sleep related movement disorders</i></b>		
Restless legs syndrome	Restless legs syndrome	G25.8
Periodic Limb Movement Disorder (PLMD)	Other unspecified extrapyramidal and movement disorders	G25.8
Sleep related leg cramps	Sleep disorders not otherwise specified	G47.8/R25.2
Sleep related bruxism	Sleep disorders not otherwise specified	G47.8
Sleep related rhythmic movement disorder	Sleep disorders not otherwise specified	G47.8/F98.4/R25
Sleep related movement disorder, unspecified	Sleep disorders not otherwise classified	G47.9
Sleep related movement disorder due to drug or substance	Sleep disorders not otherwise specified	G47.8
Sleep related movement disorder due to medical condition	Sleep disorders not otherwise specified	G47.8
<b><i>Other sleep disorders</i></b>		
Other physiological (organic) sleep disorder	Sleep disorders, not otherwise classified	G47.9
Other sleep disorder not due to substance or known physiological condition	Sleep disorders, not otherwise classified	G47.9
Environmental sleep disorder	Sleep disorders, not otherwise classified	G47.9
<b><i>Sleep disorders associated with conditions classifiable elsewhere</i></b>		
Fatal familial insomnia	Sleep disorders, unspecified	A81.8
Fibromyalgia	Fibromyalgia	M79.6-70

(Continued)

ICSD-2	ICD-10	ICD-10 Code
Sleep related epilepsy	Epilepsies	G40.0-3 (depending on type)
Sleep related headache	Not otherwise specified headache syndromes	G44.8
Sleep related gastroesophageal reflux	Gastroesophageal reflux	K21.0-9
Sleep related coronary artery ischemia	Other forms of angina pectoris	I20.8
Sleep related abnormal swallowing, choking, and laryngospasm	Laryngospasm	J38.5

## **APPENDIX B**

# Sleep/wake (side) effects of various classes of commonly used drugs

**Note:** Compounds are listed in which there is data on sleep-related side effects. The data should not be regarded as providing a rigid comparative evaluation but are intended to provide a feel for the likeliness that a drug has an effect on sleep or wakefulness and of the clinical relevance of such an effect. When drugs are not listed in this table, it does not mean that they do not have influences on sleep. Furthermore, even when drugs share a common mode of action, sleep-related side effects are not necessarily the same, due to various factors such as blood–brain barrier penetration and degrees of receptor binding. Minus (–) signs denote the severity of insomnia, plus (+) signs the severity of sedation or sleepiness, and tilde (~) signs the severity of abnormal dreams or nightmares.

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity <sup>1</sup>
<b>Benzodiazepines</b> (for clinical details, see chapter 5)	GABA-A agonism	insomnia, anxiety disorders, sedation	sleepiness, withdrawal insomnia	+++
<b>Antipsychotics</b>		—		
chlorpromazine, perfenazine > fluphenazine, periciazine	D2 antagonism [H antagonism]	—	sleepiness	+++
chlorprotixene > zuclopentixol > flupentixol	D2 antagonism [H antagonism]	—	sleepiness	+++
clozapine	D2/5HT2 antagonism [H antagonism]	—	sleepiness	+++
olanzapine, quetiapine	D2/5HT2 antagonism [H antagonism]	—	sleepiness	++
haloperidol, bromoperidol, pipamperon	D2 antagonism	—	sedation	+
amisulpride, sertindole, sulpiride	D2/5HT2 antagonism	—	sedation	+
risperidone, paliperidone	D2/5HT2 antagonism	—	insomnia, sedation	–/+
aripiperazole	partial D2 agonism	—	insomnia, sedation	–/+
tiapride, pimozide, fluspirilene penfluridole	D2/5HT2 antagonism	—	<sup>2</sup>	
<b>Antidepressants</b>				
amitriptyline, dosulepine, doxepine, nortriptyline	5HT/NA-reuptake inhibition [H antagonism]	depression, anxiety disorders, neuropathic pain	sedation, withdrawal insomnia	+++

mianserin, mirtazapine	NA-release stimulation, 5HT1 stimulation [H antagonism]	depression	sleepiness	++
trazodone	5HT reuptake inhibition, NA-release stimulation, 5HT1 stimulation [H antagonism]	depression	sleepiness	--/++
(es)citalopram, fluoxetine, paroxetine, sertraline	5HT-reuptake inhibition [5HT2 stimulation]	depression, anxiety disorders	insomnia, abnormal dreams, bruxism, yawning, sedation, withdrawal insomnia	--/++/ ~~
duloxetine*, venlafaxine	5HT/NA-reuptake inhibition	depression, anxiety disorders, *neuropathic pain	insomnia, abnormal dreams, bruxism, yawning, sedation, withdrawal insomnia	--/++/ ~~
fluvoxamine, paroxetine, sertraline	5HT-reuptake inhibition [5HT2 stimulation]	depression, anxiety disorders, neuropathic pain	insomnia, yawning, sedation, withdrawal insomnia	--/++
clomipramine, imipramine, desipramine	5HT/NA-reuptake inhibition [H antagonism]	depression, anxiety disorders, neuropathic pain	insomnia, sedation, withdrawal insomnia	-/++
moclobemide (A), selegiline (B), rasagiline (B), tranylcypromine (A, B)	MAO-A/B-inhibition	depression	insleep insomnia	--
reboxetine, bupropion	NA/(D)-reuptake inhibition	depression	insomnia	--
<b>Antiepileptics</b>				
gabapentin	calcium antagonism L-type VGCC	epilepsy, neuropathic pain	sedation	+++
barbiturates	GABA-A agonism	epilepsy, anesthesia	sleepiness	+++
benzodiazepines	GABA-A agonism	epilepsy, anesthesia	sleepiness	+++
chloralhydrate	GABA-A agonism	epilepsy, anesthesia	sleepiness	+++

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
felbamate	GABA-A agonism	—	insomnia, sedation	-/+
ethosuximide	calcium antagonism T-type VGCC	—	sedation, abnormal dreams	++/~
vigabatrin	GABA-transferase inhibition	—	sedation	++
carbamazepine, oxcarbazepine, phenytoin, topiramate, valproate, zonisamide	voltage-dependent Na-inhibition	—	sedation	++
levetiracetam	voltage-dependent Na-inhibition (SV2A-inhibition)	—	sedation	++
pregabalin	calcium antagonism L-type VGCC	neuropathic pain	sedation	-/+ +
lamotrigine	glutamate release inhibition	—	insomnia, sedation	-/+
<b>Drugs for Parkinson disease</b>				
bromocriptine, ropinirole	dopamine D2 agonism	—	sedation (sleep attacks)	++(+)
tolcapone	COMT-inhibition	—	insomnia, abnormal dreams	--/+ ++/~
biperidene, dextetamide, trihexyphenidyl	M antagonism	—	insomnia, sedation <sup>2</sup>	---/+++
pergolide, pramipexole, rotigotine	dopamine D2 agonism	—	insomnia, sedation (sleep attacks)	--/++(+)/~
apomorphine	dopamine D1/D2 agonism	—	insomnia, sedation <sup>2</sup>	-/+ +
entecapone	COMT-inhibition	—	insomnia, abnormal dreams	--/~
levodopa	dopamine precursor	—	insleep insomnia	-
rasageline	MAO-B-inhibition	—	—	—
<b>Drugs for multiple sclerosis</b>				
interferon beta-1a	interferon	multiple sclerosis	insomnia	-

### Drugs used in dementia, amyotrophic lateral sclerosis

riluzole	glutamate NMDA antagonism	amyotrophic lateral sclerosis	sedation	++
memantine	glutamate NMDA antagonism	Alzheimer disease, vascular dementia	sedation	++
donepezil, galantamine, rivastigmine	cholinesterase inhibition	Alzheimer disease	insomnia, sedation	--/+
<b>Anti-migraine</b>				
almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	5HT1 antagonism	—	sleepiness	++
eletriptan	5HT1 antagonism	—	insomnia, sedation	-/+ ++
methysergide	5HT2B antagonism	—	insomnia, sedation	--/+ ++
<b>Muscle relaxants</b>				
baclofen	GABA-B agonism	—	sedation, sleepiness	+++
dantrolene	calcium inhibition ryanodine antagonism	—	insomnia, sedation	-/+
hydroquinine	K-channel inhibition	—		
tizanidine	alpha-2 agonism	—	insomnia, sleepiness	-/+ +++
<b>Antihypertensives, vasodilators</b>				
acebutolol, betaxolol, bisoprolol, carvedilol, metoprolol, nebivolol, oxprenolol, pindolol, propranolol	beta-adrenergic inhibition, lipophilic	—	abnormal dreams	~
atenolol	beta-adrenergic inhibition, hydrophilic	—	insomnia	-
celiprolol	beta-adrenergic inhibition, hydrophilic	—	insomnia, abnormal dreams	-/~
carteolol, timolol	beta-adrenergic inhibition	intraocular hypertension	abnormal dreams	~
amlodipine	calcium antagonism L-type VGCC	—	sedation	++

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
nifedipine, nifedipine, nitrendipine	calcium antagonism L-type VGCC	—	insomnia	--
verapamil	calcium antagonism L-type VGCC	—	insomnia/nervousness	--
enalapril, fosinopril, perindopril, quinapril	ACE inhibition	—	insomnia	-
other ACE inhibitors	ACE inhibition	—	insomnia related to cough	--
acetazolamide	carbonic anhydrase inhibition	intraocular/intracranial hypertension	sedation	++
brimonidine	alpha2 agonism	intraocular hypertension	insomnia	-
moxonidine, rilmenidine	imidazoline stimulation	—	insomnia, sleepiness	-/+ + +
valsartan	AT1 antagonism	—	insomnia	-
doxazosine	alpha1-inhibition	—	sleepiness, abnormal dreams	+ +/~
prazosine	alpha1-inhibition	—	sleepiness, abnormal dreams	+/~
urapidil	alpha1-inhibition	—	insomnia	-
methylidopa	alpha2 stimulation	—	sleepiness, abnormal dreams	+ +/~
clonidine	alpha2 stimulation, imidazoline stimulation	—	insomnia, sleepiness	-/+ + +
ketanserin	5HT2 antagonism	—	sleepiness	++
sildenafil	phosphodiesterase-5 inhibition	primary pulmonary hypertension	insomnia	--
sildenafil, tadalafil, vardenafil	phosphodiesterase-5 inhibition	erectile impotence	insomnia	(-)
<b>Antiarrhythmics</b>				
amiodarone	K-channel inhibition	class III antiarrhythmics	insomnia, abnormal dreams	--/~ ~
isoprenaline	beta1/2 agonism	—	insomnia/nervousness	-



**Drugs used in hypotension,  
circulatory failure**

ibopamine	dopamine agonism, alpha-adrenergic agonism	cardiac failure	insomnia/nervousness	—
epinephrin	alpha-1/2-beta2 agonism	—	insomnia/nervousness	--
midodrine	alpha-1 agonism	—	insomnia/nervousness	—
enoximon	phosphodiesterase-3 inhibition	cardiac failure	insomnia	—
fludrocortisone	mineralocorticoid	orthostasis, adrenal insufficiency	insomnia	—
caffeine	phosphodiesterase inhibition	orthostasis	insomnia	—
<b>Lipid-lowering agents</b>				
nicotinic acid	lipolysis inhibition	—	insomnia	—
atorvastatin, fluvastatin, pravastatin	HmGCoA-inhibition	—	insomnia	--
<b>Anti-acids</b>				
calcium/magnesium-carbonate, hydrotalcite, magnesiumoxide, -peroxide, -sulphate	magnesium	—	sedation <sup>3,4</sup>	+
famotidine, nizatidine	H2-inhibition	—	insomnia	—
omeprazol	H+/K+-ATPase (proton pump) inhibition	—	insomnia, sedation	--/+ +
rabeprazol	H+/K+-ATPase (proton pump) inhibition	—	insomnia, sedation	--/+
esomeprazol, lansoprazol	H+/K+-ATPase (proton pump) inhibition	—	insomnia	—
misoprostol	prostaglandin agonism	NSAID gastroprotection	insomnia	(-)

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
<b>Anti-emetics</b>				
cinnarizine	H antagonism	—	insomnia, sedation	—/+ ++
cyclizine	H antagonism	—	insomnia, sedation <sup>5</sup>	—/+ ++
meclozine	H antagonism	—	sleepiness	++
droperidol	D2 antagonism	—	sedation	+
metoclopramine	D2/5HT3 antagonism	—	sleepiness	++
granisetron	5HT3 antagonism	—	sedation	+
aprepitant	NK1-inhibition	—	insomnia, sleepiness, abnormal dreams	—/+ ++/~
scopolamine	M antagonism	—	sleepiness	+++
<b>Anti-cough</b>				
codeine	opioid	—	sleepiness	++
noscapine	opioid (?sigmoid)	—	sedation	+
dextromethorphan	glutamate NMDA antagonism	—	sleepiness	++
<b>Antihistamines</b>				
alimemazine, promethazine	H1/M antagonism	—	sleepiness	+++
dimetindene, hydroxyzine	H1/M antagonism	—	sleepiness	+++
acrivastatine, fexofenadine, mizolastine, oxatomide	H1 antagonism	—	sedation	++
hydroxyzine	H1/M antagonism	—	sedation	+
cetirizine, ebastine,	H1 antagonism	—	sedation	+
oxememazine	H1/M antagonism	—	Insomnia <sup>7</sup> , sleepiness	—/+ +++

flunarizine	calcium inhibition VGCC [H antagonism]	—	insomnia, sedation	—/+ +
mebhydroline	H1/M antagonism	—	insomnia, sedation	—/+ +
clemastine	H1 antagonism	—	Insomnia <sup>7</sup> , sedation	—-/+
ketotifen	H1/M antagonism	—	(insomnia) <sup>7</sup> , sedation	(-)/+
desloratidine	H1 antagonism	—	(insomnia) <sup>7</sup> , sedation	(-)/+
loratidine	H1 antagonism	—	insomnia/nervousness	—
<b>Drugs used in asthmatic disorders</b>				
ephedrine	alpha-1/2 agonism	—	insomnia/nervousness	---
formoterol, salbutamol, salmeterol, terbutaline, phenoterol	beta-2 agonism	—	insomnia/nervousness	--
theophylline	phosphodiesterase inhibition	—	insomnia/nervousness	--
ipratropium, tiotropium	parasympatholytic	—	—	—
montelukast	leucotriene inhibitors	—	insomnia	—
omalizumab	FCeRI-antagonist	—	sedation	+
<b>Drugs used in urology</b>				
dariphenacine	M3 antagonism	incontinence	insomnia, sedation	—/+
flavoxate	calcium antagonism L-type VGCC (8)	incontinence	sedation	+
oxybutinine	parasympatholytic	incontinence	sedation	+
alfuzosine, terazosine	alpha-1 antagonism	retention	sedation	+
<b>Drugs used in gynaecology</b>				
dinoprost, sulproston	prostaglandin agonism	delivery induction	sedation	+
phenoterol	beta-2 agonism	uterus spasmolytic	insomnia/nervousness	---
atisoban	oxytocin antagonist	uterus spasmolytic	insomnia	—

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
<b>Antibiotics: bacterial, protozoal, helminthine</b>				
benzylpenicillin	penicillin	—	sedation	+
nitrofurantoin	—	—	sedation	+
fusidic acid	—	—	sedation	+
norfloxacin	chinolone	—	insomnia, sedation	-/(+)
ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin	chinolone	—	insomnia, abnormal dreams	-/~
clarithromycin	macrolide	—	insomnia, abnormal dreams	-/~
ertapenem	beta-lactam antibiotic	—	insomnia	-
dapsone	—	lepra	insomnia	-
clofazimine	—	lepra	sedation	+
daptomycin	—	—	insomnia	-
mefloquine	—	malaria	insomnia, sedation	--/+ +
artemether, lumefantrine	—	malaria	insomnia, sedation	--/+
atovaquon	—	malaria, protozoa	insomnia	-(-)
metronidazole	—	protozoa	sleepiness	+(+)
praziquantel	—	infestations	sleepiness	+(+)
<b>Antiviral drugs</b>				
amantadine	[glutamate NMDA antagonism]	influenza A	insomnia, sedation ("reduced concentration")	-/+
peginterferon alpha 2a, 2b	interferon	hepatitis C	insomnia, sedation, abnormal dreams	--- + +/~~

interferon alpha 2b	interferon	hepatitis B, C	insomnia, sedation	---/+ +
interferon alpha 2a	interferon	hepatitis B, C	insomnia	--
ganciclovir	DNA polymerase inhibition	—	insomnia/nervousness, sedation, abnormal dreams	--/~/+
valaciclovir	DNA polymerase inhibition	—	insomnia/nervousness, abnormal dreams	--/~
famcyclovir	DNA polymerase inhibition	—	sedation	(+)
aciclovir	nucleoside inhibition	—	sedation	(+)
peginterferon alpha 2a	interferon	—	insomnia	---
ribavirin	RNA polymerase inhibition	—	insomnia	---
entecavir	nucleoside inhibition	—	insomnia	--
ritonavir	protease inhibition	HIV	insomnia, sedation	--/+ +
emtricitabine	nucleoside inhibition	HIV	insomnia, abnormal dreams	--/~
duranavir	protease inhibition	HIV	insomnia, abnormal dreams	--/~
atazanavir	protease inhibition	HIV	insomnia, abnormal dreams	--/~
maraviroc	fusion inhibition (CCR5)	HIV	insomnia	--
lopinavir	protease inhibition	HIV	insomnia	--
lamivudine	reverse transcriptase inhibition (nucleoside)	HIV	insomnia	--
didanosine	nucleoside inhibition	HIV	insomnia	-
amprenavir, tipranavir	protease inhibition	HIV	insomnia	-
efavirenz, zidovudine	reverse transcriptase inhibition (nonnucleoside)	HIV	insomnia	-
enfuvirtide	fusion inhibition (GP41)	HIV	abnormal dreams	~
flucytosine	—	—	sedation	+

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
voriconazol	—	—	insomnia	(–)
posaconazol	—	—	insomnia	--
<b>Hormones, antihormones</b>				
testosterone	androgen	—	insomnia	--
clomiphene	estrogen antagonism	—	insomnia	–
lutropin	LH	—	sleepiness	+++
buserilene	anti GnRH	—	insomnia	–
cabergoline	D2 antagonism	prolactinoma	sleepiness	+
bromocriptine	D2 antagonism	prolactinoma	sleepiness	+
quingolide	D2 antagonism	prolactinoma	insomnia, sedation	–/+
mecasermine	IGF1	—	sleep apnoea	
thyroxines	thyroid hormone	—	insomnia/nervousness <sup>3</sup>	---
<b>Antidiabetics</b>				
exenatide	incretin-analogue	—	sleepiness	++
diazoxide	insulin secretion inhibition	hypoglycemia	insomnia	–
<b>Calcium regulators</b>				
pamidronate	bisphosphonate	—	sleepiness	++
<b>Opioids</b>				
fentanyl, hydromorphon, buprenorphin	opioid-mu-agonist	—	sleepiness	+++
morphine	opioid-mu-agonist	—	sleepiness, abnormal dreams	++/~

alfentanil, codeine, dextromoramide, dextropropoxyphen, methadone, nicomorphine, remifentanyl	opioid-mu-agonist	—	sleepiness	++
pentazocine	opioid-mu-agonist partial	—	sleepiness	++
pethidine	opioid-mu-agonist, M-antagonist	—	sleepiness	++
sufentanyl	opioid-mu-agonist	—	sedation	+
oxycodon	opioid-mu/kappa/delta-agonist	—	insomnia, sleepiness, abnormal dreams	--/+ +/~
tramadol	opioid-mu-agonist	—	insomnia, sedation	-/+
<b>Analgesics</b>				
"salicylates"	prostaglandin synthetase inhibition	—	sedation <sup>3</sup>	+
mesalazine	prostaglandin synthetase inhibition	—	insomnia, sedation	--/+
meloxicam, piroxicam	prostaglandin synthetase inhibition	—	sedation	+
piroxicam	prostaglandin synthetase inhibition	—	insomnia, sedation	-/+ +
aceclofenac, diclofenac	prostaglandin synthetase inhibition	—	insomnia, sedation, abnormal dreams	-/+/~
naproxen, sulindac, tiaprophen	prostaglandin synthetase inhibition	—	insomnia, sedation	-/(+)
indomethacin, nabumetone	prostaglandin synthetase inhibition	—	insomnia, sedation	-/+
dexibuprofen, flurbiprofen, ibuprofen, ketoprofen	prostaglandin synthetase inhibition	—	insomnia	-
etoricoxib	cyclo-oxygenase-2 inhibition	—	insomnia, sedation	-/+
celecoxib	cyclo-oxygenase-2 inhibition	—	insomnia	--

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
<b>Corticosteroids</b>				
betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone	glucocorticoid agonism	—	insomnia	--
beclomethason, budesonide	glucocorticoid agonism	—	insomnia/nervousness <sup>3</sup>	-
<b>Anti-inflammatory drugs</b>				
methotrexate	nucleoside inhibition	—	sedation/CNS toxicity	+
aurothiomalate	gold	rheumatoid arthritis	insomnia	-
infliximab	TNF-alpha-inhibition	disease-modifying antirheumatic	insomnia, sedation	-/+
adalimumab	TNF-alpha-inhibition	disease-modifying antirheumatic	insomnia	-
<b>Immunosuppressants</b>				
muromonab	anti CD3-lymphocyte antibody	—	sedation	++
daclizumab	anti Tac-leucocyte antibody	—	insomnia	---
eculizumab	anti complement C5 antibody	paroxysmal nocturnal hemoglobinuria	insomnia	--
mycophenolate (mofetil)	inosine monophosphate dehydrogenase inhibition	—	insomnia	-(-)
tacrolimus	protein kinase inhibition	—	insomnia	--
<b>Macular degeneration</b>				
pegaptinib	VEGF antagonism	angiogenesis inhibition	insomnia, abnormal dreams, nocturnal sweating	-/~



**Cytostatics: cell cycle inhibitors**

nelarabine	nucleoside inhibition	—	sedation/CNS toxicity	+++
isophosphamide	alkylating agent	—	sedation/CNS toxicity <sup>3</sup>	++
temozolomide	alkylating agent	—	sedation	++
gemcutabine	DNA synthesis inhibition	—	sedation	++
mitoxantrone	DNA/RNA synthesis inhibition	—	sedation	++
hydroxycarbamide	DNA synthesis inhibition	—	sedation	+
dexrazoxan	topoisomerase II inhibition	cardiotoxic antidote	sedation	++
etoposide	topoisomerase II inhibition	—	sedation	+
cytarabine	nucleoside inhibition	—	sedation/CNS toxicity <sup>3</sup>	+
asparaginase	L-asparagine inhibition	—	sedation/CNS toxicity	+
bortezomib	mitosis inhibition	—	insomnia, sedation, abnormal dreams	--/+/~
capecitabine, oxilaplatin	DNA synthesis inhibition	—	insomnia	--
busulfan	alkylating agent	—	insomnia/nervousness	-
procarbazine	alkylating agent	—	insomnia <sup>2</sup>	-
vincristine	mitosis inhibition	—	insomnia	-
cladribine	nucleoside inhibition	—	insomnia/nervousness	-

**Cytostatics: growth factor inhibitors**

mitotane	corticosteroid antagonist	adrenal carcinoma	sedation	+++
anastrozole	aromatase inhibition	breast carcinoma	sedation	+
aminoglutethimide	aromatase inhibition	breast carcinoma	insomnia, sedation	-/+++
exemestane	aromatase inhibition	breast carcinoma	insomnia	---
flutamide	androgen inhibition	prostate carcinoma	insomnia	-
medroxyprogesterone	progestagen	breast carcinoma	insomnia	-

(Continued)

Drugs	Primary mechanism [type II side effects]	Main indications	Sleep/Wake disturbance	Severity (1)
<b>Cytostatics: immunomodulators</b>				
bevacizumab	anti VEGF antibody	colorectal carcinoma	sedation	++
sorafenib	tyrosine kinase inhibition	renal carcinoma	sedation	++
aldesleukin	interleukin 2a, 2b	renal carcinoma	insomnia, sleepiness	--/+++
lenalidomide	TNF-alpha/IL 6-inhibition		insomnia/nervousness, sedation	---/++
alemtuzumab	anti CD52-leucocyte antibody	leukaemia	insomnia, sedation	--/++
trastuzumab	anti HER2 antibody	breast carcinoma	insomnia/nervousness, sedation	--/++
anagrelide	phosphodiesterase inhibition	thrombocytosis	insomnia/nervousness, sedation	-(+)
tretinoin	retinol derivative		insomnia/nervousness	---
rituximab, ibritumomab tiuxetan	anti CD20-leucocyte antibody	leukaemia	insomnia/nervousness	--
dasatinib, imatinib, nilotinib	tyrosine kinase inhibition	leukaemia	insomnia	--
<b>Antidotes, addictions, obesity</b>				
amifostine	anti-alkylating agent	radiotoxicity	sedation	+
naltrexon	opioid-mu-antagonist	alcohol and opioid addiction	insomnia/nervousness	---
acamprosate	glutamate NMDA antagonism	alcohol addiction	insomnia, sedation ("impaired concentration")	--/+

disulfiram	aldehyde dehydrogenase inhibition	alcohol addiction	sedation	+
nicotine, varenicline	nicotinic agonist	nicotine abuse	insomnia/nervousness	---
rimonabant	CB1-inhibition	obesity	insomnia	--
sibutramine	5HT/NA-reuptake inhibition	obesity	insomnia	--

- 
1. Insomnia (–), sedation/sleepiness (+), abnormal dreams/nightmares (–)
    - /+/~ mild/rare (0.1–1%)
    - /+ +/~~ moderate/frequent (1–10%)
    - /+ + +/~~~ severe/very frequent (>10%).
  2. Increased sedative effects of CNS-depressants.
  3. At higher doses.
  4. During prolonged treatment.
  5. CNS stimulation at high doses.
  6. Children are more sensitive.
  7. Insomnia particularly in children.
  8. High bladder affinity.

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